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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

AUGUST 1938

THE TREATMENT OF HEMOLYTIC STREPTOCOCCUS INFECTIONS AND THE NEWER APPLICATIONS OF SULPHANILAMIDE*

REUBEN OTTENBERG

THE HEMOLYTIC streptococcus ranks among the prime causes of disease. Perhaps second to the pneumococcus as a direct cause of death, it probably is more frequently responsible for acute infections than any other germ. This is particularly true if one includes not only the diseases directly due to it, such as scarlet fever, tonsillitis, erysipelas, suppuration, puerperal fever, but the possible indirect effects attributed to it, such as glomerulonephritis and the recrudescences of rheumatic fever. It is responsible for at least one fifth of all cases of septicemia.[1]

Within recent years there has been great progress in knowledge of the biology of the hemolytic streptococcus, and in the past two years, with the advent of a remarkable and highly effective chemotherapy there has been renewed activity in the study of these infections with perhaps an unfortunate tendency to think that sulphanilamide has closed the chapter. This is far from being the case. And it is important not to lose sight of the valuable advances of recent years in the biology and immunology of the streptococcus. For this reason I will discuss this subject first.

* Delivered April 15, 1938 in the Friday Afternoon Lecture Series.

Classification of Streptococci

The hemolytic streptococci form a large group of closely related organisms.[2] They are of great viability, remaining alive in air and dust for long periods of time and from five to thirty per cent of adults are carriers. The importance of the hemolytic property as a unifying biological characteristic began to be stressed at the turn of the century when blood cultures came into use for diagnosis. Brown, in his monograph of 1919,[3] used the hemolytic character as a chief differential point, classifying streptococci into alpha or viridans, beta or hemolytic, and gamma or non-hemolytic. In blood plates the clear rings of hemolysis around the colonies are characteristic. The red cells undergo complete clearing.

A great number of the earlier attempts at subdivision of the hemolytic streptococci failed because the cultural and biological characters of the sub-groups did not correspond to clinical divisions and so many separate strains were found that no grouping was possible.

In recent years, however, many of these difficulties have been circumvented by new immunological studies. Two important new classifications have been introduced, based on different principles, not mutually exclusive but supplementing each other.

The first of these, introduced by Lancefield[4] and her co-workers, is based on a simple precipitin reaction; as antigen is used a carbohydrate (often called substance C) extracted from the bacteria themselves with hot hydrochloric acid; as antibody, the serum of rabbits immunized with formolized bacteria. With this method hemolytic streptococci from all sources are found to fall readily into seven sharp groups.

Cutting across and supplementing this classification is typing by the method of agglutination. Unsatisfactory attempts to type hemolytic streptococci have been made for years. But recently by a slight simplification of technic Griffith[5] has shown that hemolytic streptococci derived from human sources can be classified by agglutination with immunized rabbit's sera into twenty-eight (or perhaps more) fixed types analogous in many ways with the fixed types of pneumococci. These strains maintain their specificity for years; certain of them have special pathological or epidemiological peculiarities.[6] Four of the types (Nos. 7, 16, 20 and 21) have now been eliminated[7] as not belonging to Lancefield's group A. The others are all pathogenic for man and are found with varying incidence in all kinds of hemolytic streptococcus

affections. It is of the greatest importance that one and the same strain may be responsible for entirely different clinical diseases.[8] Already grouping (A to G) and typing of strains (within Group A) are helping to clear up many epidemiological problems.

Before going into the hotly debated and still not entirely settled question of the specificity of certain streptococci it is necessary to say a few words about the five known toxins of the hemolytic streptococcus.

TABLE I

CLASSIFICATION OF STREPTOCOCCI

BROWN 1919 *Culture on Blood*	LANCEFIELD 1933 *Specific Precipitation*	GRIFFITH 1935 *Specific Agglutination*
Alpha (α) Viridans		
Beta (β) (Hemolytic)	A—Pathogenic; of human origin—but causing mastitis in cows by contact with human carriers—hence milk borne epidemics of sore throat and scarlet fever	Twenty-four or more permanent types, numbered between 1 and 28
	B—Chiefly bovine C—In various animals Cause disease in animals—may be harbored in human throat, vagina or intestines, but as a rule without causing disease	Four or more types known (Nos. 7, 16, 20, 21)
	D, E, F, G: Usually saprophytic found chiefly in foods	
Gamma (γ) (Non-Hemolytic)		

TOXINS

The hemolysin (often called streptolysin) is the toxin which has been known longest. It is liberated in culture media and can be assayed quantitatively. It is not limited in its action to human red blood cells but acts on the cells of many different animals. An antibody to it (antistreptolysin) frequently occurs in human disease particularly of course in hemolytic streptococcus diseases and has recently become of clinical importance.[9] Antibodies to streptolysin have been difficult to produce in animals but recently Todd[10] has shown that streptococci from human infections (Group A) have two lysins; one of these is a true toxin whose

injection leads to the production of neutralizing antibodies in animals: it is labile in the presence of oxygen. The other, like the hemolysins produced by the non-human streptococci of groups B, C, D and E, is oxygen stable and non-antigenic.

The second known toxin of hemolytic streptococci, a leukocidin, has been little studied because of difficulties of technique. It probably plays an important rôle in killing not only leukocytes but also other cells and hence probably in the local (pyogenic) effects of hemolytic streptococci.

A third toxin (if it deserves the name) is a ferment-like substance, fibrinolysin,[11] capable of dissolving fibrin. It is specific for human fibrin and is formed only by Group A streptococci. There is no evidence that it plays a rôle in the spread of streptococci through the tissues unless it does so by influencing the character of the exudate.

Until recently a soluble toxin fatal to animals had not been demonstrated in culture filtrates. But in 1934 Weld[12] succeeded in extracting such a toxin of great potency from the surface of young organisms. This lethal principle always accompanies hemolysin but is not identical with it.

The fifth and most important (from the practical view) is the erythrogenic toxin. The study of this has played a large rôle in the question of the specificity of certain strains of streptococci. While the existence of an erythrogenic toxin was presumed after the discovery of the Schultz-Charlton reaction in 1918 (blanching of the scarlet fever eruption locally on intracutaneous injection of convalescent scarlet fever serum), proof of the definite existence of a soluble exotoxin capable of producing erythema only when injected into the skin of susceptible humans was the result of the work of G. F. and Gladys Dick.[13] It is often spoken of as the "Dick Toxin". It has had the most widespread application in the prevention and treatment of scarlet fever, an application which I cannot discuss here.

The great question of the specificity of the scarlet or erysipelas toxins is still in dispute[14] with the best of authorities and arguments on each side. Since the experts cannot agree it would seem best for the outsider to accept some intermediate view, such as that put forward by Hooker[15] and by Gay;[16] all hemolytic streptococci produce more or less erythrogenic toxin, each toxin being a mixture containing different quantities of different toxin moieties. An antitoxin formed against a strain of broad polyvalency and high toxin production (such as most

strains from scarlet fever) may neutralize erythrogenic toxin from many other sources.

Such a view is capable of explaining many otherwise irreconcilable observations such as the immunity of some individuals to certain scarlet fever toxins but not to others,[17] the failure of commercial antitoxin to neutralize the toxin of some scarlet fever strains, the occurrence of scarlet fever in Dick negative persons, the permanence of immunity to scarlet fever and the impermanence of immunity to erysipelas, the undoubted efficacy of scarlet antitoxin and scarlet convalescent serum in some cases of erysipelas and other streptococcus infections, and so forth.

Serum Treatment

The multiplicity of hemolytic streptococcus strains probably forms only a partial explanation for the failure of most polyvalent antistreptococcus sera in human infections in the past. It is not very difficult to produce in horses sera which will influence streptococcus bacteremia in laboratory animals if the bacteremia is due to strains similar to those used for immunization. Such sera are usually phagocytosis-promoting rather than bactericidal or antitoxic. Even if the promotion of phagocytosis should turn out to be of great importance, the experience of recent years with type specific antipneumococcus sera shows how unlikely it is that any polyvalent antibacterial serum as yet produced can have enough antibody to be of more than occasional and accidental efficacy for organisms of such widely different serological strains as the streptococci.

What place has serum treatment then (since the introduction of sulphanilamide) in the treatment of hemolytic streptococcus infections other than scarlet fever? In actual practice ordinary polyvalent antistreptococcus serum has too little value to be further considered. In erysipelas the specific antitoxin[18] (and equally scarlet antitoxin) has considerable therapeutic effect although probably less than has sulphanilamide. The trend of recent clinical opinion is that scarlet fever convalescent serum is superior (despite lower antibody content) to the animal derived antitoxin,[19] not only in scarlet fever but in all sorts of other hemolytic streptococcus infections.[20] Such convalescent sera are not available everywhere but most of our large cities now have serum centers where convalescent sera are carefully gathered.[21] New York is fortunate in having such a center under charge of William Thalhimer.

Some may think the advent of sulphanilamide has made sera superfluous but this is not so. There are cases in which sulphanilamide has to be stopped because of idiosyncrasies. There are cases in which it is ineffective. There is also evidence that the drug and serum supplement each other: the serum is antitoxic and the drug is antibacterial: certainly they do not interfere with each other. For this reason in every desperate case of hemolytic streptococcus infection it would seem wise to supplement the drug with the serum—by preference convalescent scarlet fever serum when available.

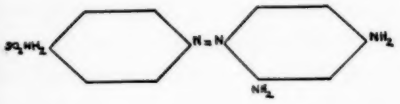
Chemotherapy

When I was asked over a year ago to give the present lecture the request was that I should discuss the then new chemotherapy for streptococcus infections. At that time the status of the new drugs was less certain than it is now and I hesitated to commit myself to present the subject a year later. For this reason I chose the non-committal title "Treatment of Hemolytic Streptococcus Infections".

However, within the past year I have had an opportunity to follow over a hundred treated cases myself, and the literature has presented an enormous amount of new information. It is perfectly clear now that for the first time a successful bacterial chemotherapy has been found. And it promises to have a far wider usefulness than originally appeared probable. In fact it is one of the major advances of our generation.

The curious round about course of progress in this field is interesting.[22] Before 1935 there had been innumerable attempts to find a chemical which would have a specific effect on various kinds of bacteria. None of these had been successful. In the majority a start had been made with some substance known to have bacterial killing properties in the test tube. Heidelberger and Jacobs[23] had pointed out that there was a certain chemotherapeutic effect from molecules containing the azo coupling, for example para-amino-benzene-sulphonamide-azo-hydrocupreine. Whether it was this or pure chance that led Domagk in 1935[24] to try the effect of the dye, prontosil (though it had no bactericidal effect in the test tube) is not known. At any rate his experiments on the hemolytic streptococcus sepsis of mice and rabbits were clear cut and conclusive and were immediately confirmed by Levaditi and Vaisman,[25] and at once led to effective use of this dye by oral administration in the treatment of streptococcus infections.[26]

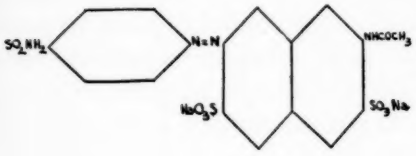
CHART I



THE *ORIGINAL* PRONTOSIL

(Prontosil rubrum Prontosil flavum Sulphonamide-chrysoidin)

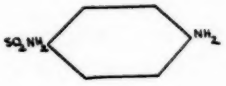
A red crystalline substance no longer in use.



PRONTOSIL SOLUBLE

Now generally called *PRONTOSIL*

A red solid usually supplied in 2½% solution (formerly known also as Streptozon)



SULPHANILAMIDE

(Prontylin, etc.)

Para-amino-benzene-sulphonamide

The original dye, prontosil, is a very insoluble substance and has the property of staining the entire body intensely. A related dye, of a much more complex structure but very much more soluble and convenient, known as prontosil soluble or prontosil solution soon replaced it. This could be given by intramuscular or, if necessary, even by the intravenous route. It had the same peculiar properties, having no effect on bacteria in the test tube but nevertheless curing experimental and clinical infections.

Within a few months a further simplification was introduced by Tréfouel[27] and associates. They found that para-amino-benzene-sulphonamide was the common factor not only in prontosil but in a large series of other more or less active compounds. With this drug, which has now been given the name of sulphanilamide, they obtained both in mice and rabbits results quite as good as those obtained with prontosil. Their work was quickly confirmed.[28]

Sulphanilamide represents about one half of the molecule of the more complex drugs, and the azo linkage which was originally thought to be essential to the therapeutic effect is not present. Sulphanilamide (intro-

duced under the trade name, prontylin), unlike prontosil, is not a new drug covered by patents, but is a long-known chemical compound which any competent chemist can make. It is now produced by a great many different pharmaceutical houses under different names. The Council on Pharmacy of the American Medical Association has recommended[29] that the name sulphanilamide be used; while a shorter name might perhaps be desirable it seems best to adhere to this name. The term prontosil when used now refers to soluble prontosil.

Fuller[30] in England and Marshall[31] and associates in the United States have cleared up some of the mystery about the effect of prontosil; both of the original forms of prontosil liberate sulphanilamide in the body and it is possible that their therapeutic effect is due entirely to the sulphanilamide liberated. Soluble prontosil liberates about one-third of its weight of sulphanilamide.

Sulphanilamide

Sulphanilamide is a colorless solid, somewhat soluble in water (0.8 per cent) but most conveniently given by mouth in the solid form. Its easy solubility in fat may turn out to have considerable significance.[32] The study of its mode of action and practical use have led to certain very important observations. In the presence of a very limited number of bacteria and a suitable environment the drug is slightly bactericidal. It is, however, unmistakably bacteriostatic; that is to say, provided the number of bacteria is not too great, it definitely slows down the rate of growth of hemolytic streptococci. It was claimed by Levaditi[33] at the very beginning that its major effect was not only on the bacteria but on the specific hemolysin and leukocidin (and by inference the other toxins of the streptococci). This has received confirmation in a recent remarkable piece of research by Osgood and Brownlee[34] in which the effect of the drug was observed on infected cultures of human bone marrow. When dissolved in broth or in salt water the drug has little killing effect on streptococci. When dissolved in the serum of such animals as the mouse or the guinea pig, which have slight natural resistance to streptococci, the drug has a distinct inhibitory effect on growth but is unable to accomplish sterilization. When dissolved in serum such as that of man and monkey which in itself has considerable bactericidal power for streptococci, the drug greatly enhances this bactericidal power so that numbers of organisms such as may occur in human infections, namely

up to 500 per cubic centimeter, are completely killed.

According to earlier work of Buttle, Colebrook and associates[35] in England and Long and Bliss[36] in this country, fairly high concentrations (1/10,000 or 10 mg. per 100 cc.) in serum are necessary to accomplish sterilization; and dosage has accordingly been adjusted to bring about such a concentration. But if the recent work of Osgood and Brownlee[34] is correct the drug is effective at a much higher dilution in human serum, only 1/100,000 (or 1 mg. per 100 cc. of serum). If this turns out to be true (and its confirmation will require further clinical as well as experimental studies) we shall require much smaller doses than we have been using.

It is probable from all the recent work that the drug does not work in the body only by direct killing of bacteria but also by neutralizing the aggressive poisons of the bacteria. Colebrook[37] at first thought that the effect depended on stimulation of phagocytosis. But the drug is bactericidal in the test tube when added to human blood from which practically all of the leukocytes had been filtered (method of Flemming). Mellon and his group have shown that even when it appears to cure infection the drug does not kill all the bacteria in the tissues. This explains the observation made almost at the beginning of the work by Levaditi[38] that in mice which had apparently recovered, recurrence of the infection and death might occur at any time from one to thirty days after administration of the drug had been stopped. Similar clinical observations have been made in man. For this reason the appropriate procedure is to continue treatment for at least four or five days after the apparent cessation of infection. Fortunately in man these recrudescences are much less frequent and serious than in mice because man has a very much higher immunity to hemolytic streptococci.

Absorption and Excretion

Within the past year careful work on absorption and excretion of the drug by Fuller[30] and by Marshall[31] have taught us much concerning the best method of administration. Absorption of sulphanilamide from the gastrointestinal tract is very rapid. In ordinary dosage most of the drug administered is absorbed in four hours. If it be possible to use the gastrointestinal tract there is no advantage in parenteral administration. By repeated administration at intervals of three or four hours the concentration of sulphanilamide in the blood can be steadily raised to five, ten,

fifteen or even more milligrams per 100 cc. of serum. Long and his associates[36] believe the blood level should be kept at ten milligrams per 100 cc. but many others[40] have obtained excellent results with lower concentrations (4-7 mg. per 100 cc.). Marshall[31] has shown that in patients with large daily divided doses it takes three days for the blood level to reach an equilibrium and a blood concentration of ten to fifteen milligrams per 100 cc. can be maintained easily. It takes about three days after the drug is discontinued for the blood to free itself if such a level has been reached.

Marshall has devised a simple clinical method of determining the concentration of the drug in the blood. Such determinations ought to be made occasionally in most cases and frequently in critical cases. Long and Bliss[36] pointed out on clinical grounds and Osgood[34] and others have shown on experimental grounds that continuous treatment is essential. The drug must not be omitted during the night. The continuous presence of low concentration in the blood is more important than intermittent high concentration. The drug penetrates well into tissue fluids, into pleural exudates, cerebrospinal fluid and hence into all the tissues but in none of these places does it reach as high a concentration as in the blood. For this reason it is frequently advisable to inject 0.8 per cent sulphanilamide (made from the pure crystalline product) in normal sodium chloride solution into the spinal fluid in meningitis and into the pleura in empyema cases.[41] In patients to whom the drug for any reason can not be administered by mouth, one has a choice between intramuscular administration of the dye solution prontosil, or the subcutaneous infusion of 0.8 per cent sulphanilamide. The question of the relative effectiveness of these two procedures is not yet settled. Certainly prontosil administration leads to a much lower concentration of sulphanilamide in the blood than does the administration of sulphanilamide directly; but it seems nevertheless to be clinically about as effective. Both drugs are rapidly absorbed when given intramuscularly or subcutaneously and it is probably never advisable to give either drug intravenously.

Both soluble prontosil and sulphanilamide are excreted rapidly in the urine; the latter is certainly excreted in the bile. This has led to valuable applications of these drugs particularly in the treatment of infections of the genito-urinary and biliary tracts. In treatment of urinary infections the concentration of the drug in the urine is important. Marshall[42] has shown that in man and the rabbit a part of the drug is excreted in

conjugation as a para-acetyl derivative while in dogs it is all excreted in its original form, that is as sulphanilamide. The important thing is probably the concentration of unaltered sulphanilamide which is easily determined by Marshall's method. With renal impairment of course the excretion of the drug is slower and the effect to be expected in urinary infections is not so great; hence the administration of the drug must be more cautious and must be checked by more frequent blood examinations on account of the possibility of its accumulating in the blood.

Dosage

It is quite possible that on the basis of Osgood and Brownlee's[34] recent work a smaller dosage than at present used will be found satisfactory. But for the present at least it will be best to adhere to the dosage worked out by Colebrook[35] and by Long[36] on essentially clinical grounds. It is important to attain the desirable concentration in the blood as rapidly as possible; for this reason a large amount of the drug should be given during the first twenty-four hours. The usual dosage of sulphanilamide is figured at approximately one gram for each twenty pounds of body weight in twenty-four hours with an average upper limit for adults of five or six grams. But during the first day of treatment in any serious case and during many days of treatment in very desperately serious cases, considerably larger doses up to a total of ten or even fifteen grams per day have been given with success.[43]

The danger of toxic effects or idiosyncrasy seems to be no more with large than with ordinary doses. After the first few days, if the symptoms are abating and there is no bacteriemia, the dosage may be reduced. Half dosage is continued for four or five days after the infection has apparently subsided.

When prontosil is used the dosage for twenty-four hours can be calculated most conveniently as one cubic centimeter of the 2½ per cent solution (obtained in ampoules on the market) for each pound of body weight except that for persons over one hundred and fifty pounds in weight it is better to reckon on three quarters of a cubic centimeter per pound. As in the case of sulphanilamide the daily dosage should be divided and given at from four to six hour intervals. When prontosil and sulphanilamide are given together a gram of sulphanilamide can be taken as approximately equivalent to twenty cubic centimeters of prontosil.

CHART II

AVERAGE DOSAGE OF PRONTOSIL OR SULPHANILAMIDE FOR SEVERE INFECTIONS

In twenty-four hours, *For every twenty pounds body weight up to 120 pounds,*

SULPHANILAMIDE 1 gram (15 grains) by mouth or subcutaneously, or interchangeably,

PRONTOSIL 20 cc. intramuscularly.

Dose should be distributed as uniformly as possible throughout the twenty-four hours, e.g., for an average adult 1 gram sulphanilamide (or 20 cc. prontosil) every four hours *day and night.*

For the first twenty-four hours in particularly dangerous infections 50 per cent or 100 per cent more may be given.

After temperature is normal half dosage is continued for five to fourteen days according to severity of the case.

Toxic Effects

The drug on the whole is remarkably non-toxic. In animals it is necessary to give almost incredibly large doses[44] to produce toxic effects or death. In human beings any toxic effect other than minor inconveniences is extremely rare.

The cyanosis which occurs with the use of the drug can hardly be regarded as a toxic effect. It occurs in over 60 per cent of all patients and is not accompanied by dyspnea or diminished oxygen carrying capacity of the blood.[45] Sulphemoglobinemia or methemoglobinemia was at first thought to be the cause of the cyanosis[46] but now is believed to be extremely rare.[47] It has been thought that the sulphemoglobinemia was due to administration of sulphates,[46] generally in the form of magnesium sulphate. The real cause of the cyanosis is unknown; it may be some black oxidation product of the drug on the surface of the red cells.[45] In general it is important to remember that cyanosis is to be expected; unless other symptoms appear it is not to be regarded as a reason for discontinuing the drug.

Certain subjective symptoms frequently occur. These are nausea, vomiting, headache, slight dizziness and mental confusion. In rare cases these symptoms are enough to prevent administration of the drug. I have the impression that they occur chiefly in nervous individuals who expect them or realize that they are getting an unusual form of treatment. They are almost never the precursors of more serious toxic symptoms and can as a rule be disregarded. They are just as likely to occur after very small doses as after large doses.

A common but not serious effect is a mild degree of acidosis.[48] This can usually be relieved by mere administration of bicarbonate of soda and in fact it is wise to give bicarbonate of soda, one gram for each gram of the drug administered as a routine in all cases.

Both in animals and in man long continued administration of the drug does not produce any delayed toxicity or late secondary effects. When the drug has been given a considerable number of days and the patient's temperature has come to normal, there is occasionally a secondary rise of temperature without further symptoms of infection. This "secondary fever" is probably due directly to the drug itself and the temperature returns to normal when the drug is stopped.[49] I have seen this phenomenon a number of times. It is very puzzling and the decision to stop the drug calls for a nice clinical discrimination.

All the other described toxic effects of the drug must be classified as idiosyncrasies, that is, as abnormal results which cannot be produced in the vast majority of cases even by very large doses. The possibility of these idiosyncrasies is important to keep in mind although they are very rare indeed; when they occur some of them are very serious.

Anemia is commonly regarded as the most important idiosyncrasy. Severe degrees of anemia are so common in almost all the infections for which the drug is used that it is often questionable whether an anemia which occurs is really due to the drug. However, there have been a considerable number of cases of acute hemolytic anemia reported.[50] Jaundice or hemoglobinuria may accompany the anemia. I have seen only one such severe case with hemoglobinuria. These cases have almost all recovered when the drug was stopped and one or two blood transfusions given but there probably have been some deaths. Anemia of the aplastic type has been described. It is extremely rare but is much more dangerous than the hemolytic anemia. Agranulocytosis must be extremely rare also, but there have been several cases attributed to the drug.[51] In animal experiments and clinical observations the drug seems to have only a very slight if any depressing effect on the leukocyte count or the bone marrow. Anemia can develop in two or three days and it is important in all cases under treatment to repeat blood counts frequently. One case of a transient optic neuritis[52] has been ascribed to the drug and one case of apparent generalized allergy (urticaria, sneezing and dyspnea).[53] There have been a considerable number of cases of a peculiar widespread dermatitis.[53,54] Rather definitely the drug sensitizes the skin to light and

dermatitis has occurred chiefly in ambulant patients who exposed themselves to direct sunlight. The discovery of porphyrin[55] (a hemoglobin degradation product capable of sensitizing to light) in the urine of these cases may explain this and perhaps other idiosyncrasies. The eruption is morbiliform, does not affect the mucous membranes, is often accompanied by fever up to 103° and usually does not persist longer than about three days even if the drug be continued. Persons who have once had the eruption are likely to get it again if the drug be resumed.[56] Some of the patients have developed it after a single small dose. Schwenkter[53] saw it in ten of 180 patients, a large proportion of them ambulant. We have seen three cases in approximately 150 hospitalized patients. On account of the rare idiosyncrasies sulphanilamide in spite of its vast usefulness must be considered a dangerous drug. Most of the accidents have occurred after small doses which shows how great a rôle special susceptibility plays. It is important that druggists should not supply this drug to the public for self medication. All patients receiving it should be under daily medical supervision, especially for the first few days of administration.

CHART III

PRECAUTIONS TO BE TAKEN DURING TREATMENT WITH SULPHANILAMIDE AND PRONTOSIL

1. Patient must be examined in a good daylight at least once a day, (for jaundice, anemia, eruptions).
2. Urine must be watched daily for hemoglobin or bile.
3. Blood count must be made every day for first three days then every two days.
4. Bicarbonate of soda must be given (in a dose about equivalent to sulphanilamide) to prevent acidosis.

PUERPERAL INFECTIONS

The earliest practical application of sulphanilamide was in the treatment of puerperal hemolytic streptococcus infections. Colebrook and his co-workers, who made the first comprehensive report in 1936,[57] have recently reviewed one hundred cases[58] and show a striking reduction in mortality, from 22.8 per cent for 495 cases in the preceding five years, to 8 per cent in the last one hundred cases. Their series included fifteen patients with positive blood cultures and six with general peritonitis, and one half or more of both these groups recovered. Not only were the recoveries greater in number but the secondary develop-

ment of parametritis (almost the rule in puerperal sepsis cases before this) was very rare, 5 per cent. It is interesting that not all the streptococci were killed off, as 48 per cent of the cases still showed them in vaginal smears at the time of discharge from the hospital. Their work has been confirmed by other workers[59] and there is no doubt that sulphanilamide represents an immensely valuable remedy in puerperal infections. It is possible that routine use of small doses after childbirth, especially in cases exposed to infection, might greatly reduce the incidence of puerperal infections since the experimental work all indicates that the drug is far more effective against incipient than well developed infections.

Meningitis

There is no field in which the effects of sulphanilamide therapy have been so dramatic and conclusive as in the treatment of streptococcus meningitis. The mortality before the advent of this drug was 95 per cent to 97 per cent according to the statistics of Neal[60] and of Gray.[61] The first recovery with prontosil treatment was reported by Caussé in February 1936 and this was followed by reports by Schwenkter, Vitenson, Neal and others.[62] Neal and Applebaum[63] reported the largest series of cases personally observed: of seventeen cases in which there was no question of the diagnosis thirteen recovered. Bliss and Long[64] reported recovery in twenty-four out of twenty-eight cases of hemolytic streptococcus meningitis with which they had had contact. This confirms the experience of other reports in the literature and indicates a recovery of something like 75 per cent of the cases.

In the treatment of streptococcus meningitis the administration of the drug must be prompt and vigorous and it is advisable (although not all authors agree that it is necessary) to give the drug intraspinally as well as by mouth or intramuscular injection. In the intraspinal administration it is important to use only the 0.8 per cent solution in saline made up with pure crystaline sulphanilamide (which can be obtained from Winthrop or from Du Pont). Prontosil has been tried intraspinally but Schwenkter[62] warns against it as it seems to be irritating and less effective than sulphanilamide. The intraspinal treatment is carried out by replacing about ten to twenty cubic centimeters of spinal fluid with sulphanilamide about twice in twenty-four hours until the spinal fluid becomes cleared of streptococci on smear and culture. Oral or intra-

muscular treatment is continued for a considerable period longer, for ten to fourteen days, or until the patient is entirely well; but for the latter part of the period the dosage can be reduced to one-half or one-third. It is important that the surgical indications should be met despite the advent of the new drug. If a suppurating focus such as mastoiditis or sinusitis requires surgical drainage, this should be carried out. It is very likely that prophylactic administration of sulphanilamide in cases in which meningitis is to be feared, such as mastoiditis or brain injuries, may reduce the incidence of this form of meningitis.

Streptococcus Infections of Other Serous Membranes

In streptococcus infections of the eye, the peritoneum, the pleura, joints and other serous surfaces, sulphanilamide has yielded extraordinarily good results. I have seen two cases of streptococcus peritonitis which recovered promptly with the drug. Three out of four cases of streptococcus pleurisy in the stage in which there was not yet frank pus have recovered under sulphanilamide therapy.[65] As streptococcus pleurisy most commonly occurs as a complication of streptococcus bronchial pneumonia, the sputum in every case of bronchial pneumonia ought to be more carefully studied for the presence of Streptococcus hemolyticus than it has been in the past. It would seem indicated to treat streptococcus bronchial pneumonia such as so commonly follows measles and influenza with sulphanilamide both because it is a streptococcus infection of the lungs and for the prevention of the frequently occurring empyema.[66] It is no longer therefore enough to get a laboratory report that there are or are not pneumococci present in the sputum but the presence of hemolytic streptococci should also be determined and acted on.

Erysipelas

From the very beginning the reports of treatment of erysipelas with the new drug have been very striking and it might safely be said that although there are occasional cases that do not respond to it, its use is the optimal method of treating the disease. Peters and Havard[66] reported on forty-seven cases in every one of which the spread of the disease was arrested in twenty-four hours and in forty-three of which the temperature was normal in forty-eight hours. The duration of the disease is regularly shortened by the drug.[67] One of the most important

uses is in the erysipelas of very young infants[65] in whom there is usually bacteriemia and a very high mortality (94 per cent). On account of the synergistic action of specific serum and sulphanilamide reported in other connections it would seem wise in severe cases of erysipelas to use both the antitoxic serum and the drug.

Scarlet Fever

There is very little evidence that sulphanilamide has any effect in scarlet fever.[65] Peters and Havard[66] reviewed 150 cases and were not able to find sufficient differences between the treated and untreated cases to demonstrate any effect of the drug on the toxic phase of the disease. However, there was a slight difference in the development of suppurative complications; 56 per cent of the untreated and only 35 per cent of the treated patients developed such complications. It is therefore possible that sulphanilamide will be of use in the more severe cases of scarlet fever as a preventive of suppurative complications. If so used, of course it should be in addition to antitoxic or convalescent serum.

Rheumatic Fever

In spite of the well established association of hemolytic streptococci with recrudescences of rheumatic fever, all the evidence at hand is that sulphanilamide and the allied compounds not only have no therapeutic effect on rheumatic fever itself[68] but also according to a recent small but very carefully studied series of cases,[69] have no effect in preventing recrudescences when used for the streptococcus infection. Indeed the toxic effects of the drug seem to be increased in rheumatic fever. In chronic arthritis likewise the drug has been disappointing.[70]

Tonsillitis and Septic Sore Throat

Every one has reported excellent results in severe cases of tonsillitis and septic sore throat as well as in suppurative sinus infections due to the hemolytic streptococcus. However, on account of the possibility of untoward reactions the drug should not be used as a routine for ordinary sore throats but should be reserved for more menacing infections. True, the idiosyncrasies are of very rare occurrence but if one were to produce an aplastic anemia or an agranulocytosis, even though only once out of ten thousand times, as the result of the treatment of a disease in itself

relatively harmless, one would be open to blame. On the other hand in a serious infection the chance of an idiosyncrasy is very small as compared with the danger of the disease.

Streptococcus Surgical Infections and Septicemia

In all varieties of surgical infections due to hemolytic streptococcus, sulphanilamide is indicated and should be used vigorously. In septicemia (for example, in sinus thrombosis) the drug has accomplished results such as have never been seen before. However, although recoveries have been reported with sulphanilamide and without operation,[71] it does not yet seem so certain that the drug will cure any given case that one is justified in omitting surgical removal of the infected focus (e.g., the infected thrombus in the lateral sinus).

The Use of Sulphanilamide in Infections Other Than by Hemolytic Streptococcus

Sulphanilamide was originally introduced as a specific for hemolytic streptococcus infections. Further laboratory and clinical investigation has shown it to have a much wider field of usefulness.

Concerning other forms of streptococci than the typical hemolytic streptococcus (beta) of Lancefield's group A, occasional infections do occur with organisms from animal sources and it is interesting that there have been reports of successful use of the drug in cases of group B but failures in groups D and G.[72] There has also been a report of the effective use of the drug in guinea pigs against a streptococcus of group C which produces a natural acute disease in these animals.[73] The drug promises great economic usefulness in bovine mastitis.[74] In infection with Streptococcus viridans and other non-hemolytic streptococci nearly all observers have reported clinical failure although the drug in the test tube is stated by Long to have an effect on some strains of the organism. Neal reported having seen one recovery in Streptococcus viridans meningitis among three cases of meningitis due to non-hemolytic streptococci for which the drug was tried. In subacute bacterial endocarditis the results have been uniformly unfavorable.

Sulphanilamide has so far had little trial for anaerobic infections. It protects mice against intraperitoneal inoculation with Clostridium welchii[75] and I have seen one striking recovery in postabortal septicemia due to the anaerobic Streptococcus foetidus of Viellon (later described

by Schottmuller as Streptococcus putridus). Good results have also been reported in gas gangrene.[75]

With Staphylococcus aureus infections there have been almost no reports of definite favorable therapeutic effects. Our own attempts with the drug in staphylococcus septicemia were all ineffective.

Pneumococcus

In pneumococcus infections Sanford Rosenthal[77] and others have shown sulphanilamide is well worth using. It has a distinct effect on the highly virulent type III[78] as well as some effect on type I[79] and other types.[80] It has a greater effect in animals than in man. In pneumococcus meningitis Neal[63] reports three recoveries among twenty clinical cases. This is not a large proportion but as these were the only recoveries seen in her twenty years' experience, the drug is worth trying. The drug and the specific serum, experimentally at least, have an additive result.[79] Hence, it would seem worth using the drug alone for pneumococcus infections for which no serum is obtainable, particularly the very virulent type III, and perhaps along with serum for other severe cases. In the use of the drug for pneumonia there is one inconvenience, namely, the pseudocyanosis due to the drug. In severe cases it is necessary to judge the degree of anoxemia by the respiratory rate and determinations of the oxygen saturation of the arterial blood rather than as usual by the appearance of the patient.

Meningococcus

Until recently animal experimentation with meningococci was rather unsatisfactory but by the new method (C. P. Miller) of injecting the organisms suspended in a protecting solution of mucin a virulent form of meningococcus peritonitis can be produced in mice. With this method Proom showed that the drug protects mice against otherwise overwhelming infections.[81] With the meningococcus (as with the pneumococcus) the drug and the immune serum combined have a greater effect than the sum of the individual effect of the two agents.[82] The use in clinical meningococcus meningitis has been so recent that there is not yet at hand a report of a large series of cases but Long reports[83] that Schwenkter has observed fifty-five cases treated with the drug with a mortality of 19 per cent as compared with a mortality of 30 per cent in a control group treated with serum. Neal[76] reports eighteen meningitis cases of which

thirteen recovered. While the case fatality is not strikingly reduced she has the clinical impression particularly in a few very malignant cases that the drug has an unmistakably beneficial effect. Its method of administration in meningitis was discussed earlier in the present paper. Recent workers however find the intraspinal administration of sulphanilamide unnecessary: this simplifies the treatment greatly.

Other Gram Negative Organisms

Concerning the influenza bacillus, Neal[83] reports the work of Provitzky who found prontosil combined with immune serum to have some curative action on the otherwise fatal infection of mice with influenza bacilli. Neal and Applebaum report recovery in one out of ten cases of influenza bacillus meningitis so treated.

The protective effect of sulphanilamide against gram negative bacilli was first demonstrated by Buttle and co-workers.[84] They showed that the drug in relatively small doses protects mice against one hundred to one thousand otherwise fatal doses of typhoid or paratyphoid bacilli. With Friedländer bacilli experimental work by Buttle was discouraging.

Helmholz[85] showed that sulphanilamide is active against B. coli, B. capsulatus aerogenes and the proteus bacillus. He pointed out in fact that the drug is effective against practically all the common urinary infections except that with the Streptococcus fecalis (variety of non-hemolytic streptococcus) and it is fortunate that we have in mandelic acid a drug which has a very pronounced effect on the Streptococcus fecalis. Sulphanilamide is peculiarly adapted to be of aid in the very common and stubborn urinary infections with bacilli of the proteus group. These organisms resist many of the ordinary urinary antiseptics because of the strong alkaline reaction which they create but the effectiveness of sulphanilamide is greatly enhanced by this very alkalinity.

The latest gram negative organism to succumb to sulphanilamide is the Ducrey bacillus. Boris Kornblith[86] has reported highly favorable results in twenty-two of twenty-three cases of chancroid.

The use of sulphanilamide in gonococcus infections is also a matter of relatively recent discovery. Surprisingly prompt cures were shown in thirteen of nineteen cases reported by Dees and Colston[87] from Johns Hopkins Hospital in May 1937, and there has been wide experimentation with the drug in practically all genito-urinary clinics since then.[88] The consensus of opinion seems to be that with oral administration of sul-

phanilamide without any other therapy a rapid cure can be expected in about half the cases. Good results have been reported in prostatitis, arthritis, ophthalmia and other complications.[89] A certain proportion of the cases seem to be resistant to the drug. What factors cause this uneven response is not yet known. Due to the fact that gonococcus cases are usually ambulant, while most of the other diseases for which sulphanilamide has been used are not, and that exposure to sunlight undoubtedly increases the susceptibility to skin eruptions, the majority of the cases which have shown skin idiosyncrasies have been reported from genito-urinary clinics. Gonorrhea is a disease which is generally curable by other means and it is possible that the drug will in the future be reserved for systemic, complicated or otherwise resistant cases of gonococcus infections.

Urinary Infections

In the genito-urinary organs the drug acts not only in virtue of its already recognized effect in the tissues, but also because of its excretion, in far higher concentrations in the urine than it ever reaches in the blood. Fuller[30] early in 1937 showed that when prontosil is given by injections, sulphanilamide is excreted in the urine (along with prontosil). In this case sulphanilamide appears in the urine only from four to six hours after the injection of prontosil. On the other hand when sulphanilamide is given by mouth it appears as such in the urine very rapidly and in very high concentrations. Marshall and his co-workers[31] showed that whereas in the dog all the drug is excreted as sulphanilamide, in man as well as in the rabbit about one-half is excreted in a conjugated form as a para-acetyl derivative and this acetylated form is stated to be almost inactive. Marshall's very delicate method of quantitative testing enables one to estimate the quantity of sulphanilamide in the urine with considerable accuracy. Helmholz and his associates[85] and Long and his associates[36] found that a concentration of 75 to 200 mg. per 100 cc. of the free drug is needed for a satisfactory bactericidal effect in the urine. It was found by Helmholz clinically[90] that the drug shows distinctly increased effectiveness in alkaline solution. The administration of sodium bicarbonate should never be omitted when the drug is given as a urinary antiseptic. The total volume of urine is naturally of importance when determining the bactericidal efficiency. Long recommends that the twenty-four hour volume be kept as nearly as possible eighteen hundred

cubic centimeters by the administration of fifteen hundred cubic centimeters of milk and four hundred cubic centimeters of orange juice. The concentration which the drug reaches in the urine will depend to a considerable extent on renal function. If optimal results are to be expected it is necessary to test this concentration frequently.

Aside from bacterial infections the drug has been tried with no success in syphilis but with definite curative results in malaria.[91]

Infections of Unknown Nature

In the future undoubtedly many more uses will be found for sulphanilamide. Modifications of it or of other drugs of greater potency or specificity will probably be discovered. In its use great stress has been laid on accuracy of bacteriologic diagnosis but on account of the unexpected versatility of the drug it seems worth using at present in any very grave infection of unknown nature. For example, I have recently seen recovery in two cases of pyelophlebitis. This is a disease the bacteriology of which is seldom discovered except at the postmortem table: then the organisms found are commonly some intestinal inhabitant such as streptococci, colon bacilli or anaerobes. In desperate cases of this kind, although the bacteriology cannot be determined, the drug is well worth a trial.

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THE MODERN TREATMENT OF DIABETES*

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THE MODERN treatment of diabetes presupposes a knowledge on the part of the physician of the principles of treatment. These principles may be thus enumerated:

PRINCIPLES OF TREATMENT

1. *Weight.* Maintain the patient at or slightly below the ideal body weight.

2. *Number of Feedings.* Divide the day's food allowance into three meals and three supplementary feedings. This will reduce the frequency of insulin reactions. Even diabetic patients who do not require insulin do better on frequent feedings. With protamine insulin, the bedtime feeding is especially necessary.

3. *Protein Requirements.* Provide one gram of protein per kilogram of body weight per twenty-four hours for adults and from two to three grams for children during their rapidly growing periods.

4. *Carbohydrate Requirements.* Provide carbohydrate somewhere in the middle range 120 to 200 grams per twenty-four hours.

5. *Fat Requirements.* Restrict fat to the least possible amount consistent with the maintenance of an ideal body weight. For the purpose of reducing an obese diabetic the fat should be limited to 50 or 60 grams per twenty-four hours and for normal weights should not exceed half the carbohydrate. If the patient is undernourished the fat can exceed this figure.

6. *Vitamin Requirements.* The deficiency in fat soluble vitamins inherent in the low fat diets should be overcome by adding vitamin concentrates to the diet.

7. *Insulin Requirements.* Give enough insulin to keep the urine sugar free without reactions. That means not more than an occasional trace of sugar.

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* Delivered March 18, 1938 in the Friday Afternoon Lecture Series.

8. *Urinalyses.* Control the insulin dosage by means of four separate daily urinalyses, not by a single specimen or a twenty-four hour specimen.

9. *Blood tests.* Blood tests are unnecessary for the control of glycosuria, but *are* necessary to detect a developing hypoglycemia.

10. *Infections* are particularly hazardous to a diabetic. Therefore avoid acute infections and eliminate sources of chronic infection.

These principles constitute a guide for the treatment of diabetes. If they are constantly kept in mind as objectives, the treatment of the disease becomes simplified and will be more successful.

Education of the Patient

The modern treatment of diabetes also presupposes the intelligent cooperation of the patient. The patient or some member of the family should know how to do three things, namely, calculate the diet; test his urine for sugar; give himself insulin.

Calculation of the carbohydrate, protein and fat content of the diet is not the burden it is commonly supposed to be. A well trained patient consumes perhaps five minutes a day at this task. A dietitian can teach a patient in one hour how to calculate his diet. Facility in making the calculations can then be acquired only by daily application to the task on the part of the patient.

For this instruction the services of a trained dietitian is advisable. If no dietitian is available, a nurse or even another diabetic patient can undertake the task. Expense to the patient is negligible compared with that necessary for nursing service in any other medical condition, for only one or two visits are required. The effort involved will be repaid many times by the increased well-being and security of the patient.

The task of calculating the diet should definitely be removed from the shoulders of the physician. It is no more the duty of the physician to calculate his dietary prescriptions than it is to compound his drug prescriptions. When this is fully recognized the general practitioner will approach the new diabetic patient with less perturbation, for the dietary requirements of a diabetic patient can be expressed in a single prescription of three figures. Indeed, the management of a diabetic fits particularly well into the work of a busy practitioner, because, when properly conducted, the patient does the routine work and the physician acts as a consultant at semi-weekly, weekly, or monthly intervals depending

on the severity of the case.

In reviewing in detail the actual management of a diabetic patient it is convenient to discuss the subject under four headings: 1) Diet; 2) Insulin; 3) Complications; 4) Significance of laboratory findings.

Diet

How does one determine the dietetic requirements of a diabetic patient? The task is really very simple. The one food substance that has to be supplied in adequate amount is protein. Existence can be maintained without fat and without carbohydrate, but protein is indispensable to life or even health. *Moreover for a given weight the protein requirement is a constant, regardless of the activity of the patient.* A 145 pound farmer working hard in the field needs no more protein than a bookkeeper of the same weight sitting at his desk, provided the farmer consumes enough carbohydrate and fat to supply the extra calories needed for his increased expenditure of energy. If, however, the carbohydrate and fat of his food is insufficient for his caloric needs, protein will be broken down for its 60 per cent carbohydrate fuel value and consequently his protein requirement will be greater than one gram per kilogram. This is expensive fuel both economically and physiologically. Carbohydrate and fat are protein sparers, and of the two, carbohydrate is safer for a diabetic than fat.

The carbohydrate and fat content of the diet may vary with the requirements of the patient, whether we desire him to gain, lose or maintain weight. Even these calculations may be avoided by adopting a standard beginning diet. This is the practice in most hospitals today.

The beginning diets employed at St. Luke's Hospital are:

Table I

BEGINNING DIABETIC DIETS*

	C	*P*	*F*	*Calories*
Adults	130	65	50	1230
Children 4 years	90	45	20	720
8 years	100	60	30	910
12 years	110	75	40	1100

* These should be increased to maintenance requirements as soon as the diabetes is controlled. A maintenance diet is one which keeps a patient at his ideal weight, and it differs for each individual. The patient's weight is the only reliable guide to his caloric needs.

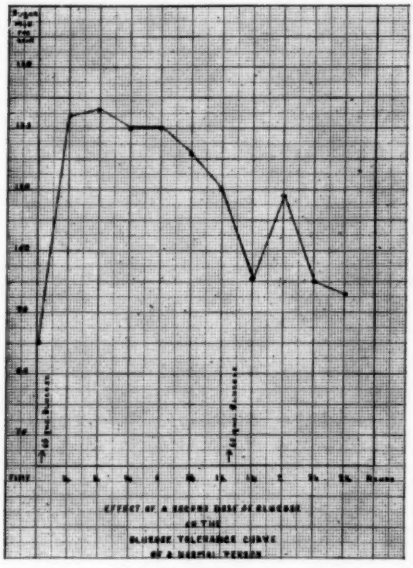

CHART I

These are beginning diets only and are usually less than the patient needs to maintain weight. When the diabetes is controlled on this diet, how are the maintenance requirements of the patient determined? Again it is a simple matter. Instead of making elaborate calculations of the patient's theoretical caloric needs, we simply weigh him once or twice weekly. If he gains weight the diet is too much, if he loses, it is too little, and if his weight remains stationary, it is sufficient. The scale on which the patient is weighed is one of the most essential instruments in the treatment of his diabetes.

The *distribution* of the food throughout the day is equally as important as the amount consumed. *All diabetics should eat between meals.* When employing protamine insulin, these supplementary feedings are especially necessary in order to avoid insulin reactions. Not only do these extra feedings prevent insulin reactions, but, by stimulating the glucose metabolizing apparatus of the body, they enable the body to handle the following meals more effectively.

This stimulating effect of carbohydrate is shown very nicely when a glucose tolerance curve is done with two doses of glucose instead of one. If a second dose of glucose is ingested during the descending arm of

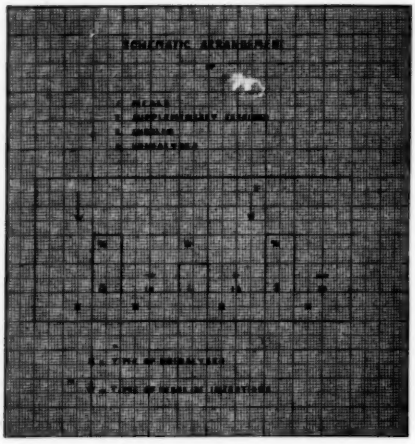

CHART II

the curve it will cause less of an elevation of the blood sugar than the original glucose feeding. (Chart I.)

The fact that carbohydrate given at one time will act as an antidote to insulin while at another it will stimulate insulin production, appears to be contradictory. The reason, of course, is that carbohydrate does not act as a stimulant to insulin production until it has raised the blood sugar to a certain critical level.

In addition to this distribution of the food into six feedings, it has been found that if the three meals themselves be divided in certain definite proportions the maximum carbohydrate load will correspond more closely with the maximum action of insulin. (Chart II.)

It is important, especially at the bedtime feeding, to give the carbohydrate in a slowly absorbing form, such as crackers, milk, cereal or even vegetables, rather than orange juice. Otherwise its buffer effect may take place too rapidly to prevent hypoglycemia in the early morning hours.

It is clear, therefore, that this distribution of food and insulin is not an arbitrary one but is based on a knowledge of the properties of the two types of insulin employed. It is theoretically sound, and yields practical results in diminished glycosuria and fewer insulin reactions.

Fluid Diet

Table II

THE "B & O" DIET

To be used during acute infections, following coma treatment and postoperatively.

C 122—P 21—F 7—Calories 635

7:00 A.M.	Orange juice,	6 ounces
9:00 A.M.	Buttermilk,	6 ounces
11:00 A.M.	Orange juice,	6 ounces
1:00 P.M.	Buttermilk,	6 ounces
3:00 P.M.	Orange juice,	6 ounces
5:00 P.M.	Buttermilk,	6 ounces
7:00 P.M.	Orange juice,	6 ounces
9:00 P.M.	Buttermilk,	6 ounces

Skimmed milk may be substituted for buttermilk, and ginger ale for orange juice with no change in food value.

Water, clear broth and tea or coffee (without cream or sugar) are allowed as desired. Insulin is given by the "color formula" with this diet.

Whenever a diabetic has a fever he must go on a *fluid diet*. Any fluid diet will answer the purpose provided the feedings are given frequently. The one which has been used successfully at St. Luke's Hospital for the past ten years consists of six ounces of buttermilk alternating with six ounces of orange juice every two hours from 7 A.M. to 9 P.M. Additional feedings are given at twelve midnight and 4 A.M. if the patient is awake. If the patient dislikes buttermilk, skimmed milk is given instead. Ginger ale may be substituted for orange juice. This diet should be given whenever the patient from whatever cause cannot take solid food. It is used postoperatively, during acute infections or even for seasickness. This diet, with the night feedings, contains about *130 grams of carbohydrate, 25 grams of protein and practically no fat.* Being low in fat it is an ideal diet for combating acidosis which usually accompanies the conditions for which this diet is prescribed. With this diet insulin is given every two to four hours by the "color formula."

Table III

COLOR FORMULA FOR GIVING INSULIN

The urine is tested with Benedict's qualitative solution every two or three hours and insulin given as follows:

If the test is orange give 15 units of insulin
If the test is yellow give 10 units of insulin
If the test is green give 5 units of insulin
If the test is blue give 4 ounces of orange juice

(Do not continue giving orange juice according to this formula if the test remains blue)

Let it be emphasized again that the management of the diet of a diabetic is extremely simple once we accept the principle that the responsibility of its calculation be transferred from the physician, who is not trained to do this work, to a dietitian or nurse or even another diabetic patient who is trained to do it. The above two types of diet are the only ones that need concern a physician treating a diabetic patient. One diet can be expressed by a prescription of three figures (keeping within the limits laid down in the principles of treatment) and the other is prescribed by the glassful.

Insulin

The introduction of protamine insulin constituted a distinct advance in the therapy of diabetes. But *protamine insulin is not a substitute for standard insulin* except in mild cases. One thing protamine insulin has done is to reduce the necessity for multiple doses of insulin in severe diabetics. For *a mild diabetic*, one dose of protamine insulin alone in the morning is sufficient. *A moderately severe diabetic* will require both protamine and standard insulin before breakfast. *A severe diabetic* needs an additional dose of standard insulin before supper. Young children may require an additional dose of standard insulin at lunch time.

A characteristic effect of protamine insulin, with or without standard insulin, is a flattening out of the twenty-four hour blood sugar curve, eliminating the peaks that occur in mild diabetics not taking insulin and in severe diabetics even with frequent doses of standard insulin (as is shown in the accompanying charts).

The importance of abolishing wide daily fluctuations of the blood sugar is emphasized when we examine its effect on the daily nitrogen balance. Wilder has shown that when the blood sugar rises above the renal threshold there is an increased excretion of nitrogen in the urine with a consequent loss of amino acids. The amino acids are the very substance from which cellular protoplasm is formed and are the precursors of the immune bodies which provide resistance to infection. This loss of amino acids undoubtedly contributes to the lowered resistance to infection of uncontrolled diabetics and the stunted growth of improperly treated diabetic children.

How does one determine the initial dose of insulin for a diabetic patient? At best the beginning dose is a guess. A safe dose with which

TABLE IV

METHODS OF INSULIN ADMINISTRATION

1. *For Regulation—*
   10 Protamine insulin
   5—5—5—Standard insulin — before meals
   Urinalyses— — four daily
   Feedings— — three meals and three supplementary feedings
   Standard Insulin— — dosage changed daily on the basis of the previous day's urinalyses
   Protamine Insulin— — dosage changed every three days as indicated by the 7 A.M. urinalysis

2. *Acidosis—*
   10 Protamine insulin

AM 7	AM 10	PM 1	PM 4	PM 7	PM 10	M 12	AM 4	
								Standard insulin

   Urinalyses— — every three hours
   Feedings— — every two hours
   Standard Insulin— — dosage changed every three hours on the basis of the color formula
   Protamine Insulin— — as above

3. *Coma—*
   50 Protamine insulin

50	40	30	20	20	20	
						Standard insulin

   Urinalyses— — every half hour
   Feedings— — glucose and saline intravenously
   Standard Insulin— — twenty units every half hour until urinalysis is "green" or blood sugar is 200 mg. per cent
   Protamine Insulin— — fifty units as the initial dose. After that once daily as in acidosis

to begin a known adult diabetic is ten units of protamine and five of standard insulin before breakfast and five units of standard insulin before lunch and supper. For young children the dose should be five units of protamine and three of standard insulin before breakfast and three units of standard insulin before lunch and supper. They are expressed respectively as $^{10}5-5-5$ and $^{5}3-3-3$. These doses are increased or decreased until the maintenance dosage is arrived at. The criteria by which the insulin is increased or decreased are the four daily urinalyses, which will be discussed later.

COMPLICATIONS

1. *Insulin Reactions*

Insulin reactions occur both with protamine and standard insulin. *Reactions with standard insulin* are apt to occur from two to five hours after injection. The treatment is ten to twenty grams of carbohydrate in the form of orange juice or sugar. If the patient is unconscious, 1 cc. of adrenalin chloride should be given subcutaneously, and glucose should be given intravenously or by stomach tube.

Reactions with protamine insulin usually occur from twelve to

twenty-four hours after injection. Because the reduction of the blood sugar is gradual over a relatively long period of time, the body becomes accustomed to the hypoglycemia and symptoms frequently do not appear until the blood sugar has fallen to 50 mg. per cent or lower. These reactions are more severe and prolonged than reactions due to standard insulin. The treatment is the same as for reactions due to standard insulin except that carbohydrate should be given repeatedly for a considerable time, ten to twenty grams every half hour for three or four hours or until the symptoms disappear.

2. *Acidosis and Coma*

Many good clinicians are now employing protamine insulin in the treatment of diabetic acidosis. In coma, an initial dose of fifty units is given followed by frequent and repeated doses of standard insulin in the conventional manner. In milder degrees of acidosis such as occur in acute infections, a morning dose of ten to twenty units of protamine insulin followed by standard insulin every two or three hours will add to the effectiveness of the standard insulin and shorten the period of acidosis. The dosage of either type of insulin must of course be controlled with frequent blood or urine analyses or both.

3. *Gangrene*

After acidosis and coma, the most important complication of diabetes is gangrene. This invariably occurs in the lower extremities and differs in no way from arteriosclerotic gangrene. In fact it *is* arteriosclerotic gangrene which occurs earlier in the diabetic than the non-diabetic.

A beginning gangrene of the toe will sometimes clear up with rest in bed and control of diabetes alone. Should the gangrene persist, surgery is indicated. An open sore of six weeks duration suggests the presence of osteomyelitis. X-ray of the toe will usually show bone destruction.

The question is whether to resort to radical or conservative treatment. In general, if the foot is warm with no pain and there is good pulsation of the arteries, conservative surgery is indicated. A moist gangrene with spreading cellulitis and lymphangitis up the leg calls for more radical surgery.

The management of the usual *acute surgical emergencies*, such as appendicitis, in a diabetic patient is a special problem. These cases are usually admitted in severe acidosis, and if possible two or three hours should be devoted to controlling this condition before operating. This

TABLE V

TREATMENT OF DIABETIC COMA

The immediate and indispensable need is fluid and sodium. These are more essential at first than insulin, because insulin is ineffective until the body fluid is restored.

Conditions to Combat:

A. Dehydration and peripheral circulatory failure (shock)

B. Acidosis

a. *Dehydration and Circulatory Failure:*

1. Physiological saline intravenously 1000-5000 cc.—glucose 5 per cent should be included in the first infusion.
2. Saline by rectum—6 ounces q.3.h.
3. Gastric lavage.
4. Clear broth, tea, coffee or water by mouth.
5. Keep patient warm.

b. *Acidosis:*

1. *Insulin*—one unit per kilogram of body weight as first dose. Then insulin is given in diminishing doses every half hour until the urine is "green" by Benedict's test or the blood sugar is 200 mg. per cent.

   50—40—30—20—20—20

   The urine is tested every half hour.
2. *Glucose* as indicated.

does not add to the surgical risk but reduces it, for these patients are often dehydrated and in shock, and measures directed toward overcoming the acidosis will at the same time combat the state of shock.

A blood sugar and CO_2 determination should be done at once. During the hour it requires to report on these, an infusion of 1000 cc. of saline is given with fifty grams of glucose and twenty-five units of insulin. After this the urine is tested every half hour, and twenty units of insulin given each half hour until the urine test is "green". In this way 105 units can be given in the two hours preceding operation, and the patient will be a much safer operative risk. A similar infusion after the operation with the same glucose and insulin is often helpful. As soon as fluids are allowed by mouth, the patient is placed on the fluid diet and insulin is given every two or three hours by the "color formula."

SIGNIFICANCE OF LABORATORY FINDINGS

The analysis for sugar of a single specimen of urine or even of a twenty-four hour specimen is of no value as a guide to insulin therapy. It merely proves that the patient has glycosuria at a particular moment or sometime during the twenty-four hours. What we want to know is after what meals is the patient spilling sugar? *In order to give insulin at the time it is needed and to avoid reactions, at least four daily urinalyses must be performed.* For the ambulatory diabetic it is sufficient to collect and analyze qualitatively a single specimen before breakfast and from

one to two hours after each meal. The before-breakfast specimen will reflect the effect of the protamine insulin given the previous day before breakfast. The forenoon, afternoon and evening specimens will detect the presence of glycosuria resulting from the corresponding meals and will indicate the necessary distribution of standard insulin if any is required. Before altering the insulin dosage a twenty-four hour record of these analyses is necessary. Therefore the *insulin dosage for any given day is determined by the urinalyses of the previous day*. It is essential to make these separate analyses every day while the insulin dosage of the patient is being adjusted. When the patient is stabilized they can be done every two or three days or even once weekly.

The urinalysis alone, then, provides a sufficient guide for controlling glycosuria or hyperglycemia. For detection of hypoglycemia, however, the urine analyses are only suggestive. With a sugar free urine hypoglycemia may or may not be present. A blood sugar analysis therefore *is* necessary to detect an impending reaction due to hypoglycemia. Indeed the chief function of a blood sugar analysis today is to prevent insulin reactions.

Again, as in urinalyses, a single blood sugar determination is of comparatively little value. In order to discover the times at which insulin reactions are most likely to occur, a *blood sugar curve* should be done. That means testing the blood for sugar several times during the day. At least four tests should be made: 7 A.M., 11 A.M., 5 P.M., 11 P.M.

This blood sugar curve need be done only once and that is when the patient has become regulated, so far as this can be determined by urinalysis alone.

In conclusion, I should like to emphasize that one needs to be familiar with only *one* diet on which to start any diabetic patient. This diet can be expressed by a prescription of three figures. One can even begin on the fluid diet, which is measured by the glassful. *Subsequent changes in the diet depend upon the weight of the patient*. The initial insulin dosage should be conservative. *Subsequent changes in the insulin dosage are determined by the four daily urinalyses*. Blood sugar tests are unnecessary while sugar is showing in the urine. When sugar disappears from the urine, the insulin dosage should be lowered enough to give an occasional "green" test. This will prevent insulin reactions. A blood sugar curve at this point is extremely helpful, but not mandatory.

HIERONYMUS MUENZER AND OTHER FIFTEENTH CENTURY BIBLIOPHILES*

E. P. GOLDSCHMIDT

London

IF IT is true that we can learn a great deal about a man by glancing over the bookshelves in his library, it is all the more certain that when by some kind chance the entire book collection of a scholar of 500 years ago has been preserved for us through the centuries, we will be able to gather quite a good deal of valuable knowledge about him, his way of life, his interests, and his work, by studying the volumes of his library.

It was my good fortune over twenty years ago, when I was working for the incipient *Gesamtkatalog der Wiegendrucke*, to stumble upon such a survival, the library of a XVth century physician who lived at Nuernberg and died in 1508. It was in the library of Prince Dietrichstein at Nikolsburg, Moravia, that I found, while cataloguing a collection of about 600 incunabula which had stood there undisturbed since the XVIIth century, that over and over again in the covers of the ancient bindings, the same owner's inscription in red ink kept on recurring, and it was soon obvious that some XVth century collection was here incorporated in its entirety. As I went on with my work, I kept track of these volumes and finally found that out of the 600, about 150 volumes bore this entry: "*Hic liber est mei Hieronymi Monetarii de Feltkirchen, artium et medicinae doctoris, quem mihi comparavi Nuremberge anno Domini 1482*"—or something like that.

Naturally, I not only made a list of these books which had remained so conveniently together, but I tried my best, off and on through the last twenty years, to find out all I could about this Dr. Monetarius, who he was, where he lived, and what he did. After all sorts of delays and vicissitudes, and after the Nikolsburg library has ultimately been entirely dispersed and scattered all over the world, I am now at last about to publish a little book on the man and his library, and thus to preserve the record at least of an interesting survival which unfortunately has not

* Read before the Section of Historical and Cultural Medicine, January 12, 1938

itself been able to withstand the upheavals of these post-war years.

I should like to tell you a little about this Dr. Hieronymus Muenzer or Monetarius, about the books he owned, about his travels, of which he left us such an interesting record, and finally, in order to show that such a standard of culture, of learning, and of book-collecting was by no means so very exceptional, about some other German physicians of the same period whose books have survived to our day.

Muenzer was born exactly 500 years ago at the town of Feldkirch in Vorarlberg, which many of us know as the frontier and passport-control station for travellers entering Austria from Switzerland. I am precise, for it is by no means *on* the frontier between Austria and Switzerland, since at that exact spot a strange oversight of history has spared to survive to this very day the independent principality of Lichtenstein. So when you leave Buchs in Switzerland and arrive in Feldkirch in Austria, your train has without warning and without stopping traversed the entire breadth—about four miles—of this very ancient state.

Muenzer came of a good family, we may presume, for his sisters married quite eminent people, but they were poor, for he tells us in one of his extant notes that it was by the help of "pious people" that he was enabled to study. He matriculated at Leipzig University in 1464 and took his M. A. in 1470; he remained another four years as a junior lecturer in the Arts course and not only maintained himself but even managed to save 400 florins in that way. We may note that Muenzer was comparatively old at twenty-seven when he first began his university studies: at that time it was quite usual for students to enter at the age of fifteen. There is a manuscript in Muenzer's library which proves that he had begun to turn to medicine before he left Leipzig, a folio volume on paper containing an extensive "Herbarius," Bernardus de Gordonio's "*De ingeniis curationum*," a brief "*Bona Anothomia*," and other medical texts; in the front cover he has noted: "*Iste liber medicinalis est mei Hieronymi Monetarii de Feldkirchen artium et medicine doctoris quem mihi comparavi in studio lipezensi anno 1470.*" It is now in the Wellcome Museum in London.

However, it was at that time considered an established fact that a first rate medical training could not be obtained in the comparatively new German universities, and only the Italian M.D. degrees of Bologna, Padua, and Pavia gave a medical man the prestige that enabled him to get into the first rank. That this state of affairs was quite officially

recognized, we can prove from a resolution passed in 1463 by the Faculty of Arts of the University of Heidelberg, by which leave of absence was granted to a Magister Nicolaus Swarczunz to go and study in the medical faculty "*que non vigeret in Almania*," "Which was not flourishing in Germany." We happen to know how it became possible for Muenzer to continue his medical studies at Pavia. In the summer of 1470 when Muenzer took his M.A. degree, a young Nuernberg patrician, Anton Tetzel, matriculated at Leipzig, and it was as this boy's private tutor, and at his expense, that Muenzer could go to Pavia in 1476 and complete his medical studies there, taking his M.D. in 1478.

Of Muenzer's Pavia period some interesting relics survive among his books. For example, one of his actual medical lecture notebooks containing the "Anatomy" of Mundinus, and considerable excerpts from Galen and Haly Abbas, "*consilia*" of his teachers, Antonio Guaineri and Ambrosio Binasco, and other matters. That he did not neglect the practical side of therapeutics for his theoretical studies is shown by a verse he entered on the flyleaf:

"*Dum dolet infirmus/medicus sit pignore firmus*
Nam si post queris/querendo hostis eris
Non didici gratis/hec musa sacra Hippocratis
Egris (imp . . .?) serviet absque dativis."

(While the patient is in pain let the doctor make sure of his reward
For if you ask for it afterwards you will only make yourself unpopular by asking.
It is not without cost that I have learned the venerable science of Hippocrates
But impecunious patients he may serve without remuneration.)

This interesting volume is now in the library of Dr. Harvey Cushing at New Haven. It is from Pavia also that Muenzer brought back some of the fine books which went to form his library, and we may assume that it was there that he first became infected with the book-collecting bacillus and that the nucleus of his library was brought together. Of course, this period, 1477-8, in which he first became financially able to spend some money on books, coincided with the first great burst of activity of the printers which brought books within the reach of people with moderate incomes.

At Nikolsburg, I found at least ten volumes in which Muenzer had noted his purchase as a student at Pavia, but there are at least about

fifteen or twenty that fall in this period. There is an Avicenna "*Canon*", 1473, a Saliceto of 1476, two works of his teacher Guainerius: "*De Febribus*," and "*De Matricibus*," 1474, the "*Pandecta Medicinae*" of Sylvaticus. The "*Antidotarium*" of Falcutius, bound with the Albucasis, both printed by Jenson in 1471, are now in the Boston Medical Library. But even then Muenzer did not by any means confine himself to medical books. There are his *Juvenal* of 1474, with extremely amusing marginal notes, now in the Yale University Library; a Lucan; a Quintilian; a Diogenes Laertius; a Sallust; the "*Cosmography*" of Aeneas Sylvius. His first book of all, perhaps, is the Aristotle, "*De Animalibus*," Venice 1476, in which he made this vivid entry recording its acquisition:

"In the year of the Lord 1476, in the last days of December, when we celebrate the birth of our Saviour and indulge in all sorts of games and pastimes, I obtained this very fine book at cards and dice. By the kindness of certain noble students of the German nation who were then studying in the faculty of Civil Law in the famous University of Pavia, at the time when Galeazzo Maria, Duke of Milan, the fifth to hold the tyranny in that principality, was killed by the dagger of a poor devil at Milan."

Immediately after leaving Pavia, the newly promoted M.D., again no doubt through the influence of his pupil, Tetzel, obtained permission to settle and practise at Nuernberg, and the appointment as one of the "Physici" of the city of Nuernberg, which I suppose corresponded to something we in England call, "Medical Officer of Health." We happen to have one of Muenzer's official reports to the City Council, made within a year of his establishment, when he gave his opinion on their enquiry whether the practise of using sulphur to clarify wine was detrimental and whether it should be prohibited. Muenzer's consilium, dated 27 October 1479, makes a great display of quotations from two dozen authorities, from Galenus and Avicenna to Gordonius and Arnoldus de Villanova, and leaves the question open. It has been preserved for us through the zeal of his friend, Hartmann Schedel (of whom more anon) in a Munich manuscript, *codex latinus monacensis 456*.

In 1480, Muenzer got married, and his only child, his daughter Dorothea, in 1499 became the wife of that Hieronymus Holzschuher whose honest face is familiar to so many people, because his portrait by Albrecht Dürer is one of the best known pictures in the world.

In 1483, a serious outbreak of the plague overwhelmed Nuernberg,

and before it was over caused about 4000 deaths in less than a year. The council immediately at the start of the epidemic, required its four appointed physicians, Hermann and Hartmann Schedel, Johannes Kraemer, and Hieronymus Muenzer to give out a kind of official notice of advice to the population how best to preserve themselves from the pestilence. This *consilium* again is extant, also through the industry of Hartmann Schedel, in *codex latinus monacensis 441*, and is quite an interesting document for our knowledge of XVth century hygiene:

"First and foremost," we read, "all the medical authorities recommend flight and to escape as soon as possible from the city and region where the pestilence is reigning, and to go far away and not to return but slowly when the poisoned air is properly clean again." For those who for one reason or another cannot escape from the city, the doctors recommend a number of prophylactic measures such as; fumigations, certain pills which you can obtain at the chemists, certain special powders also obtainable at the druggists, a special draught, etc., all these being put forth obviously without any profound conviction and seemingly more out of a friendly regard for the kindred profession of pharmacy. Anyhow, Muenzer himself, in spite of his position as official *physicus* to the city of Nuernberg, followed his own best advice and departed. He left Nuernberg on the 12th of September 1483 and went to Italy, visited Pavia again, then Bologna, Florence, Rome, and Naples, and came back in January 1484, quite pleased, as he records, to find his wife, child, and all his servants quite safe and sound on his return. He is quite frank about his motive in the brief record he has left of this little trip:

"In the year 1483, struck by the fear of a contagious pestilence, I thought that those are least likely to die in a war or in a plague who are not in them; and so, having decided to escape, I left Nuernberg in September," and so on.

Our Doctor Muenzer had been doing well in his medical practice. He tells us that in the first year he made over 500 florins, which must have been very respectable, and he could afford not only to travel but to buy some very fine books. Quite a number of them have survived and he notes in their covers that he bought his Gordonius, "*Lilium Medicine*", at Naples, his Claudianus and Solinus at Rome, his Boccacio, Theophrastus, and others at Milan.

In the following year, 1484, this time apparently without any pestilential inducement, the doctor made another little tour down the

Rhine to Aix-la-Chapelle and Belgium, allowing himself only eighteen days altogether for the trip. It is obvious that Muenzer enjoyed travelling in spite of the discomforts of journeying by mule and hack and the chances of indifferent accommodation for the night.

For the next ten years, for all we know, he seems to have remained at Nuernberg, attending not only to his practice and to his library, but also to quite extensive and definitely successful business enterprises. We learn about these trading engagements, mostly in partnership with his brother Ludwig, from the brief statement on his financial position which he drew up in 1507 shortly before his death and which is preserved in the library of the Germanic Museum at Nuernberg. That his friends looked upon him as a business-man as well as a physician, can be gathered from a letter of thanks addressed to him by Sixtus Tucher in which he hopes to hear from him "*cum a tuis mercaturae ac medicinae negociis vacaveris:*" (when you can spare the time from your medical practice and business affairs.)

In those busy years his library was steadily growing, as we can well observe by noting the dates of purchase which he generally, though not always very reliably, wrote inside the covers of his books. His interests, as we can gather from these, remained very general, and in fact it is not the field of medicine that predominates among these acquisitions after 1484. There are two special predilections we can deduce from his books. He became an enthusiastic admirer of the Platonic philosophy which was gaining such a wide following among the humanists of the late XVth century. This vogue was partly a reaction against the over-subtilised and academically over-elaborated Aristotelianism which had dominated in the European universities for two centuries; but certainly also due to the wonderful appeal the newly rediscovered and recently translated works of Plato and Plotinus made to the men to whom they came as fresh novelties, not as old textbooks read as a matter of duty in class. Muenzer obtained the first Plato in Ficino's Latin translation, of course (the Greek was not printed till 1513, and Muenzer could not have read it even if it had been available) immediately on its publication, from Florence in 1487. The Plotinus of 1492 also came to him immediately after its appearance "*ex Florentia Tuscie civitate anno Domini 1493 . . . Oh quam praeclarus et plenus philosophia hic liber est!*" And in 1494 he makes an even more enthusiastic and fervent entry in his "*Mercurius Trismegistus,*" a late Neo-Platonist treatise of mystical philosophy, which

in Muenzer's day was erroneously supposed to be of much greater antiquity than either Plato or Aristotle.

Muenzer's predilection for this type of philosophical reading matter can most strikingly be proved from his note at the end of Aristotle's *Politics:*

"This most noble book on the State written in beautiful language and full of weighty sentences, has been read through by me Hieronymus Monetarius *utriusque medicine doctor*. I read it through, I say, for the sake of recreation, in the month of May 1499, when I was suffering of a dangerous disease, and used to alleviate the intolerable pain by this very agreeable reading at Nuernberg."

The other favourite study of Dr. Muenzer, which also shows up clearly from his library, his fine Ptolemy (the rare first edition) his Solinus, his Mela, Aeneas Sylvius, and other cosmographical writers, is *Geography*. In geographical science indeed we have evidence of an interest carried beyond mere quiet study, and manifesting itself actively both by original literary work in this field, and in the doctor's unquenchable desire for travel and the visiting of unknown lands.

Nuernberg in those days was a great commercial center, one of the most important on the continent, ranking with Venice, Florence, Antwerp, Augsburg, Lyons, and Bruges. The Nuernberg patricians, who sat in the senate of their self-governing city-republic, were many of them great merchants with world-wide interests in every market from the Baltic to the Mediterranean, from Russia to Portugal; many of them had been acting as agents for their family firms in remote countries, and they were wont to send their sons out to foreign ports and fairs to watch their interests. To this type of man, the scholar who could write neat Latin verse, or make an elegant speech, or write a well-phrased letter in Latin would mean very little; but a man who from his book-learning could produce knowledge of the remote countries of the globe, of the problems of navigation, and of the courses of the stars, would give an impressive proof that something worth while was to be gained from study. We have ample evidence that in the Nuernberg of the 1480's and '90's Dr. Muenzer was looked upon as the great authority in matters geographical. And when his friend, Hartmann Schedel, prepared his great Nuernberg Chronicle of 1493, that well-known encyclopedia of historical knowledge and the most famous picture book of the XVth century, it was to Muenzer that he turned for help to bring the geo-

graphical section of the work fully up to date. I have been able to prove by examining the extant original manuscript at Nuernberg and Schedel's own copy of his book preserved at Munich, that Muenzer is responsible not only for extensive corrections and additions to the geographical section at the end, such as, for instance, the passage on Martin Behaim's voyages along the coast of Africa, but that the map of central Europe added on the last pages, is his and not Schedel's work.

Muenzer's personal friendship with Martin Behaim, the seafarer, did not only lead him to supply the account of his voyage in the Schedel Chronicle, and very probably to collaborate in the making of Behaim's famous globe of 1492, which is still extant at Nuernberg; it ultimately made him undertake his greatest personal venture, his journey to Spain and Portugal in 1494-5, of which he has left us such an interesting account. Behaim himself is rather a mysterious and unsatisfactory person. The younger son of one of the foremost Nuernberg patrician families, he ran off to sea as a boy. He certainly did succeed in accompanying Diogo Cano and his Portugese sailors on a voyage along the African West Coast in 1484, and was knighted by the King of Portugal on his return. That, however, is all we know of his practical experience as a navigator, and on his globe, however beautiful and picturesque it may be, there is little evidence of any unusual knowledge either of Africa or any other part of the world. It is quite obvious, though, that he succeeded in impressing his Nuernberg friends with his tales of adventurous exploration, and, on the other hand, the Portugese authorities with his claims to profound astronomical and mathematical learning, for he was made a member of the *Junta dos Mathematicos*. Anyhow, whether he was an impostor or not (and Muenzer's experiences tend to show that he was), he induced Muenzer to write a very remarkable letter to King John of Portugal, dated Nuernberg, 14th July 1493. In this letter, the doctor recommends that the King should send out an expedition to sail westwards across the Atlantic Ocean and so to reach the Indies and Cathay, and he suggests Martin Behaim as a suitable captain for such an enterprise. He supports his theory with quotations from Aristotle, Seneca, and Pierre d'Ailly, and points to other indications, such as the existence of elephants both in India and in Africa, and the driftwood washed up by the sea on the western shores of the Azores, to prove the proximity of land in the west.

This extraordinary letter, which has such striking similarities to the

famous letter Toscanelli wrote in 1474 to a Portugese friend, would indeed have made our Dr. Monetarius a famous man, if it were not unfortunately a fact, which he could not know on July 14th when he wrote his letter, that Columbus had returned from his first voyage on March 4th. And even if he had known of Columbus' discovery of a few more islands in the western sea, this would not have affected his views any more than Columbus' own, for even on his third voyage the explorer was still endeavoring to reach Cathay, unaware that what he had stumbled upon would prove such a serious obstacle to that voyage.

Anyhow, it is clearly not unconnected with such projects that Muenzer in the following summer, 2nd of August 1494 to be exact, set out on his journey to Spain and Portugal, and had an audience with King John at Evora in November. But although he has left us a very detailed account of these interviews—he was four times asked to dine with the King—there is not a word on Behaim in this or anywhere else in the "Itinerary," and it looks as if that name, which seemed to him so powerful at Nuernberg, had lost its glamour when brought out at the Portugese court.

I obviously cannot give now an adequate or even a brief account of the varied and vivid interest of Muenzer's travel diary, in which he has left us a record of his journey from Nuernberg via Switzerland, Lyons, the Rhone valley, Perpignan, Barcelona, Seville, Madrid, Granada (quite recently conquered from the Moors), to Lisbon, and back via Sant' Iago de Compostella, Toulouse, Poitiers, Paris, Bruges, Cologne, and so to Nuernberg. He returned about Easter, 1495. It is a most valuable document, and it is astonishing that it should not hitherto have been published in its entirety. The principal and no doubt most exceptional portion of it, that relating to Spain and Portugal, was printed in the original Latin in the "*Revue Hispanique*" in 1920, and after that in both a Spanish and a Portugese translation; and it amounts to about two-thirds of the whole text which occupies 416 pages of the Munich manuscript in which it has survived. The rest—that is the journey from Nuernberg to the Spanish frontier and back from the Pyrenees to Nuernberg—has not yet been edited, and I am hoping to see it printed this year in a French periodical, "*Renaissance et Humanisme.*" Of course, although unedited, the manuscript has by no means remained unknown; it has been frequently used and referred to, and little extracts have been given ever since Kunstmann, in 1854, wrote about it in the *Transactions of the*

Bavarian Academy and particularly quoted from it all that refers to the Spanish and Portugese discoveries. Naturally, with his keen interest in geographical matters, Muenzer had noted a good deal which he had heard about the overseas countries, especially West Africa, from navigators and merchants, but unforunately we seem to have lost a special discourse of his, "*De insulis*," to which he refers, but which was either never written, or has gone astray. It is interesting to note that one of the people he met in Madrid and who gave him a letter of recommendation on his way, was the Benedictine monk, Bernard Boil, who accompanied Columbus on his second voyage.

It does not seem that Muenzer brought back any books with him from Spain or Portugal. Anyhow none have survived at Nikolsburg; but he did buy some books for his library in Paris where he remained for ten days in the Spring of 1495. His account of Paris is one of the most detailed we possess of that period and should be most valuable for the local historians and topographers of that city; it is odd that it has never yet been printed.

Not much remains to be said on the remaining years of Muenzer's life; he seems to have continued quietly at Nuernberg, doctoring and collecting books until his death in 1508. Shortly before that, he visited his native town, Feldkirch, and gave a considerable part of his library to St. Nicholas Church there, a donation of which a few volumes have indeed survived, but of which we have a complete list in the Feldkirch archives, which enables us to complete the total of Muenzer's library with at least the titles of the books which have disappeared. On the same occasion, Muenzer established certain charitable trusts at Feldkirch, and an annual Mass which he endowed was indeed punctually said on his anniversary until quite recently.

Muenzer's *Itinerarium* has not come down to us in his autograph; the only copy we possess of it, the Munich manuscript, is written in the hand of his friend, Hartmann Schedel, the author of the "*Nuernberg Chronicle*." You may have noticed that, again and again, I have had to refer to things like Muenzer's report on the adulteration of wine or on the measures against the plague, as surviving in some manuscript written by Schedel. This may give you just an idea of the immense amount of most varied material whose survival and existence we owe to the industrious pen of Hartmann Schedel. Schedel, Muenzer's close colleague as official *physicus* of the city of Nuernberg, was indeed a prince of book-

collectors and a champion copier of books. He not only bought all books printed or manuscript he could get hold of, but, with indefatigable zeal, seized every opportunity to copy anything he could borrow or otherwise obtain. Schedel's famous library has been luckier than Muenzer's; about 350 manuscripts and 500 to 600 printed volumes of his still remain intact in the Munich Library, of which indeed they form the original nucleus. Comparatively few volumes have strayed from the fold, but one magnificent specimen at least is in the United States, his Petrus de Abano (Hain, No. 1), which is in Dr. Harvey Cushing's great library at New Haven. There also, you will find his copy of Nicolaus Leonicenus' book on Syphilis (1497), but it is rebound in XIXth century calf. It is surely remarkable and significant that two prominent physicians in one city and at the same time should have been great bibliophiles, and in a way, I suppose, I must beg your pardon for speaking first and at such length about my own pet discovery, Hieronymus Muenzer, rather than about Schedel, whose library was about four times the size and infinitely more important than Muenzer's. But Schedel's library has been well known and indeed famous for many years, long before Stauber's monograph on "*Hartmann Schedel und seine Bibliothek*" came out in 1908, while the minor star, Muenzer, has remained undiscovered and unknown. And if I am now able to demonstrate the existence of a closely analogous though less overwhelming second humanistic library in a Nuernberg physician's house before 1500, this fact will help us to recognise that Schedel's was by no means an isolated phenomenon, and that indeed the possession of a noble library was a fairly normal distinction of a successful German medical man of the Renaissance period.

Hartmann Schedel, unlike Muenzer, was the son of a Nuernberg patrician family, born at Nuernberg in 1440, and the cousin of another book-collecting physician, Hermann Schedel, whose books he inherited. Schedel also began his studies at Leipzig, where he entered at the normal age of sixteen, and took his M.A. in 1461. He continued his medical studies in Italy, not at Pavia but at Padua, where he took his M.D. degree in 1466. He has left us an interesting account of an "Anatomy," the very exceptional dissection of a corpse, held at Padua on March 20th to 24th 1465, under Dr. Antonio Bernardi, not without mentioning that ultimately the corpse was buried with great reverence and ceremony. On his return to Germany, he held appointments as town physician at Noerdlingen and Amberg before he settled down to practise in his

native city in 1484. He died a few years later than Muenzer, in 1514.

Schedel's best known achievement, of course, is his famous "*Chronicle*," which was published by Anton Koberger at Nuernberg in 1493 in a double edition in Latin and in German, illustrated with the same woodcuts, 2000 copies of each being printed; this is a tremendous and unprecedented number for a XVth century publication. The whole enterprise was exceptional in its scope, and took about eight years to prepare, requiring the financial backing of two at least of the richest Nuernberg merchants. The illustrations alone—there are 1809 of them—took years to design and engrave, and we know that the studio of Michael Wolgemut, where Dürer had been an apprentice, was fully occupied with them over a long period. The book as it came out, must be acknowledged to be a complete and successful realization of the object aimed at: a popular encyclopaedia of all historical knowledge, beginning with Adam and Eve, giving an account of all the Emperors and Popes, of the foundation of all the principal cities of the world, with a view of them, of all the most famous men and women, with their portraits if possible, and not only carrying the tale of events right down to the date of publication, but even providing six blank leaves for the entering of any further important happenings until the Day of Doom; this and the Last Judgment are again fully recounted and illustrated, bringing the gigantic work to an appropriate and final conclusion.

This magnificently illustrated "World-Chronicle" must not be judged as a piece of original historical research, nor must we tax Schedel with credulity for including in it all the ancient and mediaeval mythical lore about pagan heroes and Christian saints, about strange wild tribes, and the legendary origins of cities. His aim was to include everything that was popularly known and current about the world and its history, not to provide a scholarly reference book. And although the "Nuernberg Chronicle" is not unprecedented as a world chronicle, except in the magnificence of its production, and its models: Bergomensis' *Supplementum Chronicarum*, and the Luebeck *Rudimentum Noviciorum*, can clearly be recognised, it did require a scholar of wide reading and one with an encyclopaedic library at his disposal to produce the result.

From the fact that Hartmann Schedel undertook it, and from the efficient way he carried it out, we can deduce the bent of his interests. History and Archaeology were his favourite subjects, and what we can deduce from his work on the "*Chronicle*," we find confirmed when

we analyse the surviving books in his library. Of course, Schedel also had his shelves full of medical books and even a notable number of important and early medical manuscripts; the classics, the great Latin poets and prose writers both of antiquity and of the Renaissance were there in even more impressive completeness than in Muenzer's library. Indeed, the two collections are very similar in a way, and not only do we find copies of the same edition in both libraries in about 100 cases, which shows that the two friends had about the same source of supply but that they even employed the same bookbinders. Both Schedel's and Muenzer's books have mostly survived in their solid original bindings, and we see generally the same tools and the same decorations used on the majority of them. Roughly, one might say that Schedel had nearly every book that Muenzer owned in either the same or a similar edition, but he had far more than Muenzer; and it is just in the field of history, of old chronicles, annals, local and general historical works, that Schedel's library clearly outdistances Muenzer's. These historial books, moreover, were mostly not available in printed editions, and Schedel did not confine himself to purchasing such manuscripts, but with indefatigable industry wrote and copied such texts wherever he could find them. Of Schedel's 350 manuscripts now at Munich, probably nearly half are written in his own beautifully clear calligraphic handwriting. They form an unexhausted store of the most heterogeneous texts. In his eager zeal, Schedel not only copied entire historical works, or the monastic annals he found in the different abbeys, but letters, speeches, rhymes and verses, epitaphs and inscriptions, in fact almost anything which could be transferred by pen to paper. It is through Schedel's passion for writing that we have Muenzer's "*Travel Diary*," and Ciriaco d'Ancona's most precious collection of Roman inscriptions, mostly since destroyed, and an untold number of more or less important historical documents. Every year almost, one might say, some historical scholar manages to attract a little attention by publishing some text "hitherto unedited" from one of Schedel's manuscripts. If Schedel knew how much valuable historical material modern scholars have quarried from his manuscripts, and how they rather condescendingly smile at his tremendous "*Nuernberg Chronicle*," I do not think he would be either surprised or hurt. He consciously undertook the "*Chronicle*" as a work for the popular dissemination of historical knowledge, and would have been quite satisfied to let his immortality rest on his achievements as a book-collector and

antiquarian.

Schedel then is a second and even greater book-collecting physician living at the same time and in the same town as Muenzer; another great bibliophile and doctor of the XVth century was born in the same little Alpine town as Muenzer: Dr. Ulrich Ellenbog. Born at Feldkirch about 1430, he studied at Vienna where he took his B.A., at Heidelberg where he graduated M.A. in 1455, and finally finished his medical studies at Pavia, under Guainerio and Matteo dei Gradi, taking his M.D. in 1459. He was thus at Pavia twenty years earlier than Muenzer, though not so very much older. In 1460, he settled first in his native town Feldkirch to practise, where he stayed till 1468, and where he wrote a treatise "*De balneis*" on medicinal baths, extant in a Vienna manuscript. From 147? on, he was appointed physician to the bishop and chapter of Augsburg, and resided there and at Memmingen until his death in 1499. Ellenbog's fine library of beautifully bound and kept books was bequeathed by him to the Benedictine abbey of Ottobeuern, where one of his sons had entered as a monk, and was kept together there until fairly recently. It was dispersed, however, by the Munich book-trade within the last twenty years, unfortunately before anybody had taken the trouble to note its contents while it was still intact. It would be difficult now to track down all the scattered volumes of which one very fine specimen again is in Dr. Harvey Cushing's library: a "*Pharetra Doctorum*" printed by Mentelin without date, but before 1474, the date on which Ellenbog purchased it, as he notes in the front cover. Being unable to say anything precise on the size and exact contents of Ellenbog's library, all I can affirm is that all his books I have ever seen (certainly over twenty) are finely printed big folios in their old white pigskin bindings, generally bearing a number of interesting marginal notes in his hand. There are three points, however, we know about Ellenbog which make him a far from shadowy figure for us, and indeed a most interesting and significant personality. Firstly, it was he, who on the foundation of the Bavarian University of Ingolstadt, was called upon to draw up the statutes of their medical faculty; but although he was appointed the first professor of medicine there, he does not seem to have cared for teaching, and returned to Augsburg in 1473. Secondly, he was not only a book-collector and a bookish person "*scribendi impiger*" and "*perpetuae lectionis*," as his son recorded about him, but he took a very important part in the establishment of one of the first printing presses at Augsburg,

that in the monastery of St. Ulrich and Afra. There is a volume containing five Augsburg *incunabula* in Cambridge University Library, bound up for Ulrich Ellenbog in 1476 and full of his autograph notes. It is from these notes that Robert Proctor, in one of his "*Bibliographical Essays*" (1905) says: "Ulrich Ellenbog and The Press of St. Ulrich at Augsburg" has reconstructed the interesting facts about the collaboration of the abbot, the doctor, and a journeyman printer, in setting up this important press which printed among other things a 'Vincent of Beauvais'.

Thirdly, there is among Ellenbog's medical writings—most of them small treatises of a few pages of the usual type—consilia about the plague and how to guard against it, "*De simplicibus*," "*De venenis*," and that sort of thing; one most remarkable pamphlet, a "*consilium*" dated 1473, in German, entitled: "*Von den giftigen besen Tempffen un Reuchen der Metal; als Silber, Quecksilber, Bley und anders . . .*"

"On the poisonous and noxious Vapours and Fumes of metals, such as Silver, Mercury, Lead, and others, which those of the noble craft of goldsmiths and other artisans who work with fire have to contend with. How they ought to deal with them and how to get rid of their poisons."

This pamphlet, which got printed at Augsburg about fifty years after it was written, gives a brief but quite correct account of the injuries to health threatening metal workers who expose themselves to lead or mercury vapours, to nitric and other acids, and warns also against coal-dust and coal-vapours; it indicates a few simple remedies.

However slight, this pamphlet is the earliest ever written in the field of industrial hygiene, and, as such, a remarkable starting-point of a discipline of tremendous importance and consequence. Only a few years ago, in 1932, an English scholar, Dr. C. C. Barnard, gave a translation of it in the *Lancet*.

Clearly the fact that Ellenbog wrote such a pamphlet suffices to clear him of the imputation generally made against mediæval physicians, that they were men of mere book-learning, and shows him as a medical practitioner very fully alive to the problems of the world around him.

If Muenzer could be characterised as the geographer and traveller among the XVth century German book-collecting doctors, Schedel as the historian and assiduous copyist, Ellenbog as the originator of industrial medicine, what is there we could briefly say to label Burchard

von Horneck, who left his splendid library with 183 manuscripts to the bishop and chapter of Wuerzburg in 1522? He must have lived to a great age, for he graduated at Padua certainly before 1466, and in fact in 1509, Trithemius called him "grandævus." His books, both printed and manuscript, are still largely preserved in Wuerzburg University Library, and hence the best notice of him will be found in a Wuerzburg dissertation of 1907: Ignaz Schwarz: *Die medizinischen Manuscripte der Koeniglichen Universitaets-bibliothek Wuerzburg.* Few of them have strayed from there, sold as duplicates no doubt, but I do know two in the British Museum and an early printed Pliny in Dr. Harvey Cushing's library. He owned all the standard Italian XVth century medical textbooks, either printed or in manuscript, and his Latin classics prove him to have been a keen reader of general literature on humanistic lines. He wrote quite a few little books: a poem, "*De ingenio sanitatis*," twice printed in the XVth century, and another poem on St. Patrick's Purgatory, also extant in print. Among those works of his which survive only in manuscript there is a puzzling treatise, "*Contra pestem inguinariam*," discovered by Sudhoff in the Salzburg library and dated 1475. If that date is right, this treatise is a first-rate piece of evidence for those who contend for an earlier origin of syphilis than the Naples-war of 1494.

But unfortunately, nothing about this good Dr. Burchard von Horneck seems to be very reliable. He owned a manuscript of Camerino's well-known treatise about the plague, in which he has scratched out the author's name, substituting his own. In his fine manuscript of Montagnana's "*Definitiones terminorum medicinalium*," he has inserted a heading stating the book to be addressed: "*ad dominum Brocardum de Horneck Alamannum scolarem novellum diligentissimum filium suum amantissimum*"; it is certain, however, Montagnana was dead before Burchard came to Padua. So I am afraid one distinctive epithet we might give to Burchard von Horneck is that he was a liar.

An interesting group of fine incunabula from the library of another German doctor, Nicolaus Pol, is preserved now in the Cleveland Medical Library. There are about thirty of them, all in their old bindings, and bearing in their covers in very bold script the lettering: "Nicolaus Pol Doctor 1494." In spite of a good deal of endeavour, both on my part and on that of others, we know comparatively little of this Dr. Pol. He must have had a very fine and pretty large library, of which the Cleveland group is only a fraction. The majority of his books were housed in

an insignificant little Franciscan convent at Innichen (now San Candido) in the Southern Tyrol (now in Italy), immediately before they came on the market. But on my pre-war survey for the *Gesamtkatalog*, I also met them in quite considerable numbers in several monastic libraries of the Northern Tyrol, round Innsbruck, which accords with the attested fact that he was physician to the Emperor Maximilian I, who lived a good deal at Innsbruck. The date in his books is always 1494, whatever the date of impression; I now possess a book printed in 1511, with this inscription. This date can therefore not refer to the date of acquisition, and the most plausible explanation is that it is the date of his doctor's degree: Nicolaus Pol, Doctor 1494. But so far, his name, as far as I know, has not been found in any matriculation lists, and we do not know where he graduated. The only thing besides his fine surviving books, that we do know of Dr. Pol, is that he was the author of a treatise, "*De Morbo Gallico*", first printed in 1530. But we do not even know whether he was still alive when that book came out. I have never seen a book as late as 1530 with his ownership mark; in fact the 1511 book I just mentioned is, I think, the latest I have ever seen, and the majority of the Pol books are incunabula, including the splendid *Ketham* now in Cleveland.

We cannot possibly conclude a discourse on German medical book-collectors without at least a brief mention of the foremost of them all: the greatest, the earliest, and, as the founder of a still existing great library, the most consequential: Amplonius Ratingk, the founder of the Collegium Amplonianum at Erfurt, and donor of its famous library. He belongs to a very much earlier generation than any of the preceding, having been born about 1363 at Rheinberg near Xanten in the Rhineland. So his earliest youth falls into the period before the establishment of any universities in Northern Germany, and he acquired the basis of his great learning and the earliest books for his library, at places like Osnabrueck and Soest where he also taught and copied manuscripts. His first teacher in Medicine seems to have been Tilmann von Syberg, court physician to Archbishop Frederick III of Cologne. The first university within the Holy Roman Empire was Prague in Bohemia, founded in 1363, and that is where Amplonius Ratingk took his bachelor's degree in 1385, his M.A. in 1387; it is likely that he also studied at Vienna, and it is certain that in 1401 he visited Italy, but only briefly.

Ratingk was associated with both the newly founded universities of

Cologne and of Erfurt from their very inception, and although he seems to have resided chiefly at Cologne, his principal benefactions went to Erfurt where he was Rector from 1393 to 1395, and where he took his M.D. In 1412 Ratingk founded his college, the Collegium Amplonianum, at Erfurt, and kept on adding to its endowment until his death in 1435.

Amplonius Ratingk was a book-collector in the grand style, who not only kept a staff of copyists writing books for him continuously, but who went travelling about himself in the pursuit of books; we know, for instance, that he went to Bruges in Flanders to acquire a collection of forty manuscripts from the executors of the estate of a prelate, and we know that he bought books continually both from Paris and from Italy.

From 1410 to 1412, before handing over his library to his college, he himself drew up its catalogue, which is still extant, as well as the books themselves, at Erfurt in the "*Amploniana.*" It lists 640 manuscripts which are arranged in twelve classes:

1. Grammatica (36 volumes); 2. Poetica (37); 3. Logica (27); 4. Rhetorica (12); 5. Mathematica (which includes Music, Astrology, Magic, and Necromancy: 73 volumes); 6. Philosophia Naturalis, including Alchemy (64 volumes); 7. Metaphysics (15 volumes); 8. Philosophia Moralis (35 volumes including Sallust, Cassiodorus, Vegetius, Cicero); 9. Medicine (101 volumes); 10. Civil Law (7); 11. Canon Law (16); 12. Theology (213 volumes).

This library catalogue is not only remarkable for its extent and for its systematic arrangement; it even comprises the express mention of titles wanted "*quae volumina Dei adiutorio procurabuntur.*" Amplonius also drew up the statutes and regulations for the use of his library. Only post-graduate members of the Collegium Amplonianum had a right to be admitted; graduate members of other colleges had to apply to the Dean for admission. Loans were permitted, but carefully regulated, and the library was to be open from eight to one o'clock. Readers were admonished to be "*fideles in libris.*"

The Bibliotheca Amploniana with its manuscript treasures still exists, and it numbers now 978 manuscripts having both suffered losses of its ancient stock and gained accessions in the course of the centuries. It is a wonderful monument to a great man who was certainly one of the founders of scientific university studies in Germany, and a glory of the medical faculty of which he was a member.

LIBRARY NOTES

BOOK REVIEW

Klebs, Arnold C. *Incunabula scientifica et medica;* short title list from *Osiris* (vol. iv). Reprinted.

Bruges, The Saint Catherina Press, 1938. [iv], 359 p. Issued as no. 1 of the History of Medicine series under the auspices of The New York Academy of Medicine. $5.00.

As stated in the introduction this work is offered primarily as a survey, "in the briefest possible terms", of the incunabula still extant on scientific and medical subjects. As such, it is a model of conciseness, accuracy, and arrangement for future bibliographers. As a pioneer in the field of subject bibliography for 15th century books, Dr. Klebs had many things to determine, such as arrangement, inclusion of contents, and above all what to leave out so that his main purpose would stand out clearly. The arrangement is by author, or, if anonymous, by a keyword. Serial numbers are given only to the titles, of which there are some over 1,000. Editions are arranged under the titles, each given the title number followed by a decimal point and number, as: 115.1, 115.2 for editions one and two of title 115; there are some 3,000 editions in all. If an edition contains more than the main title would imply, the contents are fully listed following the entry; an added entry, in its proper alphabetical place, is made for each item, as listed, of the contents. The contents and added entries are in a smaller type and are readily distinguished from the main entries.

The work is preceded by a good seven-page list of bibliographical references arranged according to the abbreviation used for each of them. Fifteenth century authors are noted, generally speaking, for the variety of forms under which their name has appeared in bibliographies. Dr. Klebs has wisely kept the variant forms of such names from encumbering the main list by adding at the end of the book a seventeen-page list of "Cross References", referring from variant forms of an author's name to the one which he has chosen to use. Dr. Klebs has quite uniformly used the vernacular form of the name. while some would prefer to use the Latin form, especially when the author's writings were entirely, or largely in Latin.

The subjects include science and medicine in the broadest sense. Some 800 editions are miscellaneous works, of which nearly one-half are prognostications and "practica"; medicine, the largest class, has 850 editions; natural philosophy (botany, zoology, etc.) 400 editions; technology, with arithmetical, alchemical, agricultural, architectural, and musical tendencies, some 300 editions; astronomy, and of course astrology, some 200; and mathematics, including geometry, physics, etc., about 100 editions. A good many would have liked to have seen the work arranged by subject; others would have liked to have had Dr. Klebs include the valuable information which his knowledge and research must have had at hand; either, or both, of those arrangements would have detracted from Dr. Klebs' objective: a survey "in the briefest possible terms". It is hoped that Dr. Klebs' information will become available, possibly in a new and enlarged edition by subject.

Incunabula has probably received more attention from bibliographers than any other group or class of books, generally from the typographical approach with bibliographical descriptions. Very seldom has it been attempted from the subject side, especially to include the whole output of a particular subject. It is good to see one of Dr. Klebs' ability contributing so much to subject bibliography through his researches. Only

one who has worked considerably with this material can appreciate the immense amount of labor, research, and learning that has gone into this book, and the care that has been taken. Klebs 808.15 Prognostications, 1494, and 808.011 Prognostications. Practica (German) 1494, both imperfect, are apparently copies of the same edition and should be entered under Michael de Wratislavia, as the Huntington Library copy, also imperfect, fortunately has the leaf with title in which the author's name appears. Under Beroaldo, Filippo. *Declamatio philosophi, medici, oratoris,* Hain 2961a may also be added as a 16th century imprint.

A few items in the Huntington Library may be suggested as additions to the work, as follows: *Calendarium,* 1486-1504. Venice, Zeninger, 26 July 1486, a broadside; *Ephemerides, Anno Christi domini 1490* [Basel, Kesler, 1489]; *Kalendar, mit astrologischen bemerkungen,* Augsburg, Balubirer, 1481, a variant of Klebs 569.1; *Sententiae uberiores ex scripti Thomae et Alberti super Physica Aristotelis* [Leipzig, Kachelofen, about 1498-1500]; Urso, *De somniorum expositione* [Paris, Gering, about 1483]: Versor, Johannes, *Questiones super metaphysicam Aristotelis cum textu* [Cologne, Quentell, about 1493].

H. R. M.

RECENT ACCESSIONS

"Possession does not imply approval"

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DEATHS OF FELLOWS

ABEL, JOHN JACOB: Johns Hopkins University, Baltimore, Maryland; born in Cleveland, Ohio, May 19, 1857; died in Baltimore, Maryland, May 26, 1938; graduated in medicine from the University of Strassburg in 1888; received the degree of Doctor of Science from the University of Michigan in 1912, the University of Pittsburgh in 1915, Harvard University in 1925, and Yale University in 1927; the degree of Doctor of Laws from the University of Cambridge, England in 1920; elected an honorary Fellow of the Academy November 18, 1926.

Dr. Abel was professor emeritus of pharmacology at the Johns Hopkins University, having joined that institution in 1893. Prior to this, he was lecturer and professor of materia medica and therapeutics at the University of Michigan.

He was a member of the Association of American Physicians, the American Physiological Society, Society for Pharmacology and Experimental Therapeutics, American Chemical Society, Honorary Member of the Philadelphia College of Pharmacy, and Fellow of the American Association for the Advancement of Science and its President in 1931.

Dr. Abel received the first award of the Lectureship of the Kober Foundation of the American Association of Physicians in 1925, the Willard Gibbs Medal of the Chicago Section of the American Chemical Society in 1926, and the gold medal from the Society of Apothecaries, London, in 1928.

He was Editor of the Journal of Pharmacology and Experimental Therapeutics and contributed numerous works of research on animal tissues and fluids, and on the physiological and therapeutic action of various substances.

BURLINGHAM, ROBERT: 860 Park Avenue, New York City; born in New York City, February 29, 1888; died in New York City, May 28, 1938; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1914; elected a Member of the Academy November 8, 1934. Dr. Burlingham was a member of the American Medical Association and the State and County Medical Societies.

CRIGLER, LEWIS WEBB: 653 Park Avenue, New York City; born in Crawford, Mississippi, June 26, 1876; died in New York City, April 30, 1938; graduated in medicine from the Vanderbilt University School of Medicine, Nashville, in 1899; elected a Fellow of the Academy February 8, 1910.

Dr. Crigler was surgical director of the Manhattan Eye, Ear and Throat Hospital, ophthalmological surgeon to the New Rochelle Hospital and consulting ophthalmological surgeon to the Elizabeth A. Horton Memorial Hospital at Middletown and the United Hospital at Port Chester.

He was a Fellow of the American Medical Association and a member of the American Academy of Ophthalmology and Otolaryngology and the State and County Medical Societies.

HANSEN, EJNAR: 2 East 54 Street, New York City; born August 23, 1870; died in New York City, May 13, 1938; graduated in medicine from the University of Maryland in 1904; elected a Fellow of the Academy February 5, 1914.

Dr. Hansen was a Fellow of the American Medical Association and a member of the State and County Medical Societies.

HARVEY, THOMAS WILLIAM: 59 Main Street, Orange, New Jersey; born in New York City, September 10, 1853; died in Orange, New Jersey, April 8, 1938; received the degree of Bachelor of Arts from Princeton College in 1875 and graduated in medicine from the College of Physicians and Surgeons in 1878; elected a Fellow April 1, 1897.

Dr. Harvey was consulting surgeon to the New Jersey Orthopedic and the Orange Memorial Hospitals.

He was a Fellow of the American College of Surgeons, the American Medical Association, the American Climatological Society, the New Jersey Surgical Society and the County and State Medical Societies of New Jersey.

HORN, JOHN: 104 East 40 Street, New York City; born in New York City, September 7, 1856; died in Monterey, Massachuetts, June 11, 1938; graduated in medicine from New York University Medical College in 1885; elected a Fellow of the Academy May 2, 1901.

Dr. Horn was consulting surgeon of otology and rhinology to the Lenox Hill Hospital.

He was a diplomate of the American Board of Otolaryngology, a Fellow of the American College of Surgeons, and a member of the American Laryngological, Rhinological and Otological Society, the American Medical Association and the County and State Medical Societies.

MABBOTT, JOHN MILTON: 27 Washington Square, New York City; born in Waterbury, Connecticut, July 14, 1862; died, July 1, 1938; graduated in medicine from the College of Physicians and Surgeons in 1884; elected a Fellow of the Academy March 1, 1894.

Dr. Mabbott was a member of the State and County Medical Societies, the American Medical Association, the New York Obstetrical Society, the Society of Alumni of St. Luke's Hospital and Consulting Physician to the Northern Dispensary.

PETERSON, FREDERICK, 555 Park Avenue, New York City; born in Feribault, Minnesota, March 1, 1859; died in New York City, July 9, 1938; graduated in medicine from the University of Buffalo Medical School in 1880; elected a Fellow of the Academy January 3, 1888.

Dr. Peterson was a member of the State and County Medical Societies, the American Medical Association, the American Psychiatric Society, the American Neurological Society, the New York Neurological Society, and the New York Psychiatric Society. He was also Consulting Alienist to Bellevue, Central Islip and Manhattan State Hospitals, and Consulting Neurologist to the Neurological Institute and Craig Colony Hospital.

STEDMAN, THOMAS LATHROP: 1060 Amsterdam Avenue, New York City; born in Cincinnati, Ohio, October 11, 1853; died in New York City, May 26, 1938; received from Trinity College the degrees of Bachelor of Arts in 1874 and Master of Arts in 1896; graduated in medicine from the College of Physicians and Surgeons in 1877; elected a Fellow of the Academy May 6, 1880.

Dr. Stedman was surgeon to St. Luke's Hospital from 1876 until 1879 and surgeon to the New York Orthopedic Hospital and Dispensary from 1881 until 1886. He was a Fellow of the American Medical Association and a member of the County and State Medical Societies.

Dr. Stedman was the author of a medical dictionary and a number of medical handbooks. He was also the editor of many textbooks.

ANNOUNCEMENTS

1. Stated Meetings

The President and Council of the Academy, no less than the Committee on Medical Education, have long been concerned with the gradual decline of interest in the Stated Meetings on the part of the Academy membership. The program for the coming year is the issue of that concern, for it has been designed to provide meetings which no member desirous of keeping abreast of medical affairs can well afford to miss.

Even a cursory examination of this program will reveal the care exercised by the Program Committee in the selection of subjects of current interest and speakers qualified to present authoritatively the various aspects of these topics. A notable innovation for the coming year is the provision for consideration of controversial issues by invited commentators. In certain instances, discussion of the papers of the evening has been devised to invite conflicting opinions upon measures now before the medical profession.

The Committee has fixed as its objective, a program that will appeal to the Academy membership. The lack of interest recently manifested by the membership may be regarded as an indictment of this Committee; but the Committee feels that a lack of response by the Academy members to the evening programs for the Stated Meetings of 1938-39 will definitely be an indictment of the membership.

The complete program for these Stated Meetings follows. This notice refers only to the first Stated Meeting of each month. The program for the second Stated Meeting each month is arranged by the Harvey Society.

PROGRAMS

October 6, 1938

Evaluation of sulfanilamide therapy

1. Fundamental problems of chemistry and pharmacology—mechanism of the action, E. K. Marshall, Jr., Baltimore

2. Clinical aspects, Reuben Ottenberg
Discussion: Emanuel Applebaum (Meningitis)
Homer F. Swift (Rheumatic fever)
William E. Studdiford (Gonorrheal condition; postpartum infection)
Francis G. Blake (Erysipelas)

December 1, 1938

Serum therapy in pneumonia

1. Present status of serum therapy, Russell L. Cecil
2. Results with rabbit serum, Colin M. MacLeod
3. Program for meeting the pneumonia situation, Wheelan D. Sutliff
Discussion: Edward Tolstoi
Jesse G. M. Bullowa
Ralph S. Muckenfuss

January 5, 1939 — ANNUAL MEETING

Chronic gastritis

1. Recent advances in diagnosis by gastroscopy, Rudolf Schindler
2. Clinical aspects, Burrill B. Crohn

February 2, 1939

Vitamins with special reference to therapy

1. Vitamin A, Arthur M. Yudkin, New Haven
2. Vitamin B, Norman Jolliffe
3. Vitamin C, Gilbert Dalldorf, Valhalla
Discussion: Arthur J. Patek, Jr.
Soma Weiss, Boston
Philip Finkle

March 2, 1939

Symposium on arthritis

1. Gout, Philip S. Hench, Rochester, Minnesota
2. The nature of hypertrophic arthritis (degenerative joint disease), Walter Bauer, Boston
3. Evaluation of newer methods of therapy, Ralph Boots
Discussion: Philip D. Wilson
Edward F. Hartung
Albert B. Ferguson

May 4, 1939

Recent advances in the treatment of peripheral vascular disease

1. Clinical manifestations, Irving S. Wright
2. Medical treatment, Edgar V. Allen, Rochester, Minnesota
3. Surgical treatment, Reginald H. Smithwick, Boston
Discussion: Beverly Chew Smith
James C. White, Boston

2. The Eleventh Annual Graduate Fortnight

"Diseases of Blood and Blood-Forming Organs"

OCTOBER 24 TO NOVEMBER 4, 1938

The attention of the Academy members is invited to the admirable program which has been arranged for the coming Graduate Fortnight by the Committee on Medical Education.

The subject has definite interest for the physician and the surgeon and also includes phases which will interest specialists in each of these major fields.

The Fortnight Committee merits the appreciation of the membership for the judgment manifested in the selection of speakers and topics, and for the excellent composition and integration of the program for the evening meetings.

The Director of Clinics and the Hospital Committee, composed of representatives of eighteen hospitals in the Metropolitan area, have arranged for afternoon clinics, thereby providing for clinical demonstrations of every phase of the general subject.

The response already received by the Director of Exhibits gives promise of an exhibit which will equal the really remarkable one assembled last year.

The Committee is receiving so many requests for programs from all parts of the United States that it is apparent that the Fortnight has become an event of interest to the medical profession of the entire country. The Academy quite naturally welcomes the widespread interest in this undertaking, the purpose of which is essentially the dissemination of knowledge of advances in medical practice. The Officers of the Academy, however, particularly desire in this significant project the interest and sympathy of its membership.

PROGRAM OF EVENING SESSIONS

October 24, 1938

Macrocytic anemias

1. General aspects of the etiology, diagnosis and treatment, George R. Minot
2. Macrocytic anemia of sprue and allied conditions, C. P. Rhoads
3. Neural manifestations and their treatment, Maurice B. Strauss
4. Differential diagnosis and some observations concerning treatment, Cyrus C. Sturgis

October 25, 1938

Anemias due to iron deficiency

1. Etiology of iron deficiency, Clark W. Heath
2. Iron deficiency anemia in infancy, Louis K. Diamond
3. Iron deficiency anemia in pregnancy, Maurice B. Strauss
4. Concluding remarks on iron deficiency anemias, George R. Minot

October 26, 1938

Refractory group of anemias and the granulocytopenias

1. Aplastic and hemolytic anemias, C. P. Rhoads
2. The neutropenic diseases, Roy R. Kracke

October 27, 1938

Blood formation and destruction—hematohistology

1. On the origin and developmental potentialities of blood cells, William Bloom
2. The reticulo-endothelial system, Harrison S. Martland

October 28, 1938

Diagnostic procedures

1. Diagnostic significance of changes in erythrocytes, Russell L. Haden
2. Diagnostic significance of changes in leucocytes, M. M. Wintrobe

October 31, 1938

The leukemias and leukemoid states

1. Infectious mononucleosis, John R. Paul
2. A clinical and pathological discussion of the common and unusual types of leukemia, Claude E. Forkner

November 1, 1938

Malignant diseases of the lymph nodes and bone marrow

1. Certain practical aspects of Hodgkin's disease and allied disorders, Henry Jackson, Jr.
2. The general pathology of lymphosarcoma, James Ewing

November 2, 1938

The polycythemias

1. Polycythemia, Paul Reznikoff
2. Diseases of the blood in infancy and childhood, Thomas B. Cooley

November 3, 1938

The hemorrhagic diseases

1. The Wesley M. Carpenter Lecture: Hemophilia, William H. Howell
2. Classification and treatment of purpura, Nathan Rosenthal

November 4, 1938

Diseases of the spleen and therapy

1. The medical-surgical splenopathies
   a. Introduction, Allen O. Whipple
   b. Hemolytic jaundice, William P. Thompson
   c. Congestive splenomegaly, Louis M. Rousselot
   d. Thrombocytopenic purpura, Robert H. E. Elliott
2. Irradiation therapy in the blood diseases, Lloyd F. Craver
3. Concluding remarks, Charles F. Tenney

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